

UCSF MAGAZINE

Could psychedelic therapy go mainstream?



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After decades of being pushed to the fringes, research into the healing powers of psychedelics is undergoing a renaissance.



Stefan Friedrichsdorf aims to change how modern medicine cares for kids in pain.



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Blossoming Science

Could microbes or mushrooms represent the future of medicine?

Scientists across UCSF are striving to find out. Some are studying the teeming world of microbes that live in and on our bodies, while others are researching hallucinogens – both plant-based and synthetic. Their pursuits could lead to powerful new ways to treat some of the most intractable diseases.

One illness these scientists have set their sights on is depression.

In a first-of-its-kind-in-the-U.S. study, researchers at UCSF's Weill Institute for Neurosciences are investigating whether psilocybin, a compound found in fungi commonly known as magic mushrooms, can effectively ease depression and anxiety in patients with Parkinson's disease. These patients tend not to respond well to antidepressants or anti-anxiety medications, so this approach could prove life-changing for them.

Another way to tame depression could involve our microbiome. Scientists at the Benioff Center for Microbiome Medicine are examining how gut bacteria might affect brain function and contribute to either depression or mental health. Their findings could pave the way for microbial drugs tailored to a patient's individual biology.

The field of modern microbiome medicine began only about 15 years ago, and psychedelics research is starting to flourish again after decades of governmental restriction. Given UCSF's legacy of pursuing innovation to improve human health, it's no surprise that our scientists are at the forefront of both areas. Our researchers had to summon vision and determination to conduct UCSF's first psychedelic therapy trial. Our microbiome scientists had to delve into the unknown just to identify the trillions of



Robin Carhart-Harris, PhD, a prominent psychedelics researcher who is studying how psilocybin rewires the brain, is one of the UCSF scientists contributing to the booming field.

microorganisms inhabiting us, much less to decipher their myriad roles in health and disease.

Now, their curiosity and drive are yielding promising results, as you will learn in the following pages.

I am proud of the discoveries unfolding in these labs and clinics. I also look forward to what this work will one day mean for patients with conditions ranging from PTSD to multiple sclerosis to cancer. I hope you will feel the same after reading this issue.

Sam Hawgood, MBBS
Chancellor
Arthur and Toni Rembe Rock Distinguished Professor

EDITOR

Anne Kavanagh

FEATURES EDITOR

Ariel Bleicher

SENIOR CREATIVE DIRECTOR

Audrey Feely

ART DIRECTOR & DIGITAL STRATEGY

Stephanie Koch

SENIOR DESIGN ADVISER

Nada Hansen

COVER DESIGN CONSULTANT

Pentagram

VIDEO PRODUCTION

Walter Zarnowitz

CONTRIBUTING WRITERS

Jess Berthold, Katherine Conrad, Elizabeth Fernandez, Melinda Krigel, Laura Kurtzman, Suzanne Leigh, Robin Marks, Alexis Martin, Dana Mathes, Jeffrey Norris, Lexi Pandell, Elizabeth Preston, Jill Sakai, Cameron Scott, Christina Hernandez Sherwood, George Spencer, Stacy Torres, Janet Wells, Sarah C.P. Williams

COPY EDITORS

Dana Cook Grossman,
Mark Goldstein

PRINTING

Lane Press

ASSISTANT VICE CHANCELLOR, EXTERNAL RELATIONS

Jane Feledy

EXECUTIVE DIRECTOR, ADVANCEMENT COMMUNICATIONS

Cyril Manning

UCSF Magazine is published twice a year by the UCSF Office of University Development and Alumni Relations.

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CONTACT US

UCSF Magazine, UCSF Box 0248
San Francisco, CA 94143
415/476-3480
alummag@ucsf.edu

WEB
magazine.ucsf.edu

Five Questions for Diane Havlir

Diane Havlir, MD, UCSF's Weiss Professor, an AIDS pioneer, and an infectious disease leader, is partnering with the local Latinx community to protect vulnerable San Franciscans from COVID-19 and other diseases.

What is Unidos en Salud?

It's a partnership between UCSF scientists, public health experts, and Latino Task Force leaders that we formed in April 2020 to offer vital COVID knowledge and care to the Latinx community. The name means "united in health." We provide service and science for several diseases in a low-barrier, walk-up clinic in San Francisco's Mission District. We've administered over 90,000 COVID tests and 60,000 vaccinations. We've also collaborated with the DeRisi Lab at the Chan Zuckerberg Biohub to track SARS-CoV-2's evolution.

How have you achieved such success with vaccinations?

People are motivated when their questions are answered respectfully by medical experts and trusted community members. Clients are vaccinated in a welcoming environment. And we activate social networks by inviting clients to be vaccine ambassadors with family and friends.



Fun fact: Havlir was the U.S. national short-track speed-skating champion in 1974.

Why address diseases beyond COVID?

Positioning COVID services in a multidisease "big tent" reduces the stigma of visiting a COVID site. Offering other health services also generates demand. Someone may want a diabetes test or a flu vaccine, and while at our site they realize they are also due for a COVID booster. With the recent outbreak of mpox (previously known as monkeypox), we were able to rapidly add vaccination services without starting from scratch.

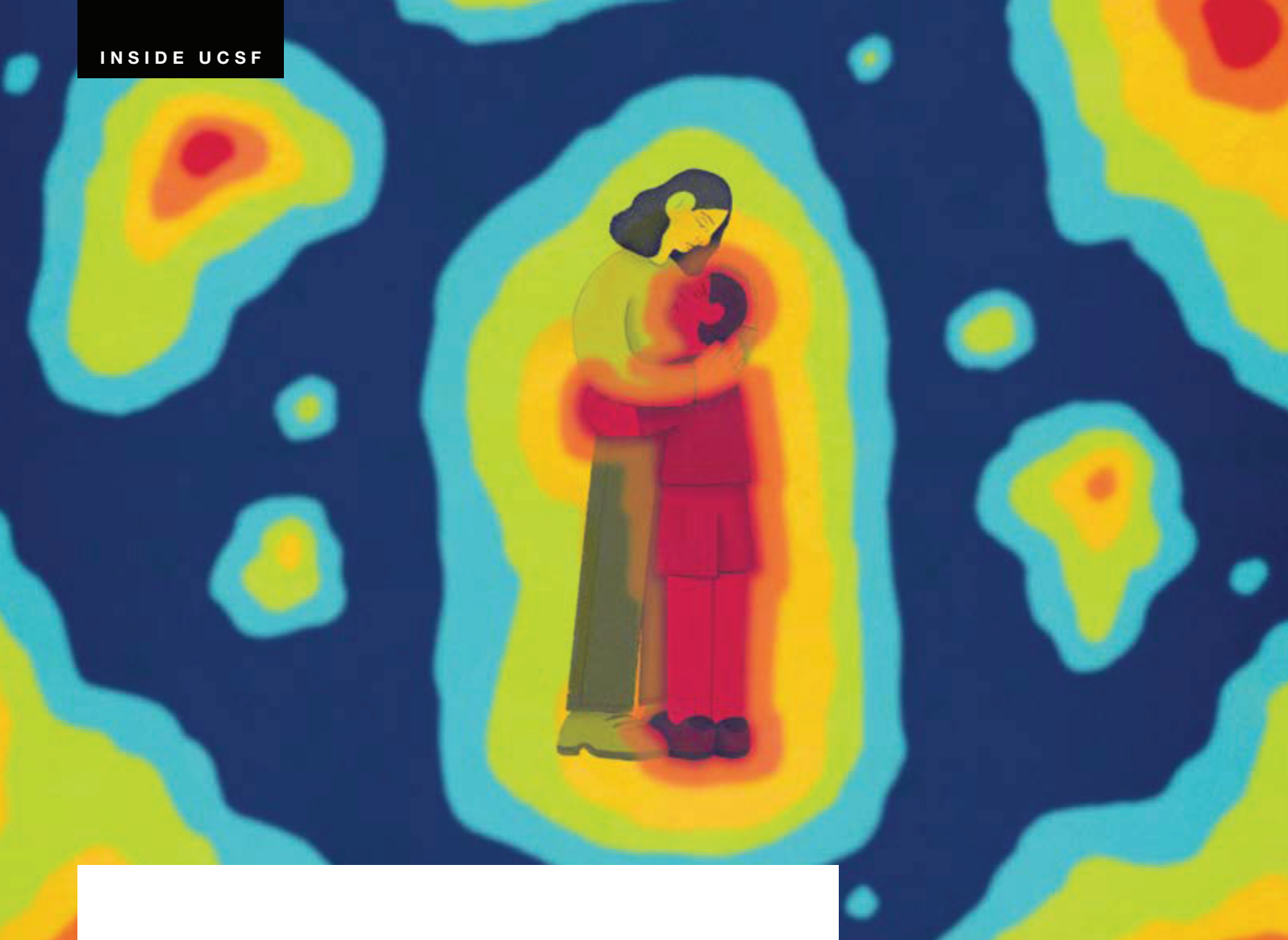
What have you learned about your community partners?

They are inspirational. Their organizations immediately mobilized to address issues such as food security, housing, employment – all critical to health. They willingly participated in our repeated crash-course updates on SARS-CoV-2 to share the information with their members. Many did all of this outside of their full-time jobs.

What motivates you?

Improving health and well-being through science and compassion – that's the reason I became a physician. This mission is shared by Unidos en Salud's passionate team.





How Can We Help Kids Cope with Anxiety about Climate Change?

We spoke with Ellen Herbst, MD, a UCSF psychiatrist and mother of two, about how the climate crisis is impacting the mental health of children and adolescents – and what parents can do to help.

By Alexis Martin

When did you start thinking about this?

It started with my older son, who is now 13. When he was in fourth grade, he learned in science class about the reports from the Intergovernmental Panel on Climate Change. He came home devastated. He was crying and feeling hopeless. He was saying, “What’s the point?” and “No one cares.”

I realized that this crisis is a huge burden for young people. Children are, appropriately, being educated about climate change in many schools and learning about it in the news, but they’re not necessarily given the coping skills to handle that devastating information.

What did you do?

As an adult psychiatrist with expertise in traumatic stress, I know that the climate crisis impacts my patients. But with my own two kids, I just felt stuck. I wasn’t sure how to tell my child that he was right: Things aren’t cer-

tain, and they may not resolve how we want them to. I decided to educate myself about how, as a parent, I can support my kids.

What did you learn?

I learned that this is not an isolated experience. My son was communicating what many kids are feeling: betrayal, uncertainty, and disempowerment. Some are terrified.

A study recently came out that surveyed 10,000 young people in 10 countries. Across this diverse sample, the majority of respondents were worried about climate change, reporting feelings like sadness, anxiety, anger, and helplessness. These are grief-related emotions. What struck me is that climate grief and distress are becoming universal, particularly for youths.

We know that low-income communities and communities of color in developing countries are disproportionately affected by the climate crisis. People in these areas are experiencing acute trauma related to losing their homes, a sense of safety, even loved ones. Then there are kids who are experiencing chronic impacts during and after climate disasters, like poor air quality or insufficient schools or buildings that are damaged beyond repair. Communities closest to the crisis deserve resources, time, and serious attention.

Kids like my son are coping with an existential dread. He hasn't lost his home; he hasn't lost loved ones. But he feels like the clock is ticking. We know a great deal about how to cope with the effects of acute disaster and trauma, but the existential grief related to climate change is a new phenomenon that also requires our attention.

How do we help our kids cope?

An emerging area of inquiry, including here at UCSF, is around building psychological resil-

ience to climate change. That means being able to cope internally, so when a child is faced with disturbing information or worrisome realities, they have a way of grounding themselves, of continuing to function, of not going straight to despair. They can live with this heavy knowledge and still reach their potential and thrive.

There are many ways of promoting resilience in kids. It might involve spending time in nature with other kids who care as deeply as your child does. For some children, climate activism can be gratifying. It could involve writing a letter to a policymaker, starting a school club, or restoring a wildlife habitat. Social activities set in nature can help a child feel more connected and like they're making a positive impact. Age-appropriate mindfulness practices can also help.

My kids and I participated in an activity with Nature in the City. We restored a butterfly habitat in San Francisco's Sunset District. Both kids really loved it because it involved a direct connection with nature. It felt like we made a concrete, positive impact.

We also try to talk about what we can do during our regular conversations as a family, as opposed to ruminating on the worst-case scenarios. That has made a difference. And we talk about the disproportionate impact that this crisis has on the most vulnerable communities.

What's your advice for parents?

Kids, especially younger children, often think in black and white. If they read a news article or climate report, they may think the world is ending. I try to explain that it's not all or nothing. If some species and ecosystems are saved, that matters.

It is also so important to remember that the primary need of a child is to feel safe. If we cannot provide that within the external world, we must try to promote safety between the parent and the child. So be honest with them. Tell them that you're not sure what's going to happen but remind them that you care and will be there with them, no matter what.

Ellen Herbst, a UCSF resident alum, is a clinical professor of psychiatry at the UCSF Weill Institute for Neurosciences and a staff psychiatrist for the San Francisco Veterans Affairs Health Care System. The views expressed here do not reflect those of the U.S. government or the Department of Veterans Affairs.



Improving Kidney Transplant Odds for Black Patients

When kidney function is calculated to place patients on kidney transplant waiting lists, an adjustment has historically been made to account for presumed racial differences in metabolic function. But a new study shows that outcomes for Black patients improve if the race adjustment is removed.

"The earlier a patient is wait-listed prior to kidney failure, the higher priority the patient has in getting a transplant and the more likely a patient could potentially avoid dialysis," says Elaine Ku, MD, MAS '15, a UCSF associate professor of medicine and first author of the paper reporting the finding. "Patients who avoid dialysis, or do it for a short period, generally have better outcomes than those on dialysis in the long term," she says. The work was led by UCSF and Hennepin County Medical Center in Minneapolis.

The researchers compared Black patients with white patients on the basis of how much time passed between their becoming eligible for the transplant waitlist and their reaching kidney failure. Removing the race adjustment for Black patients resulted in a reduction in their time on the waitlist, to a duration more similar to that of white patients.

TIPS FOR COPING



1. Spend time together in nature.
2. Get involved in climate activism.
3. Explore mindfulness practices.
4. Talk as a family about what to do.
5. Remind them that you're in it together.

CANCER MOONSHOT

PRESIDENT JOE BIDEN



Jill Biden (left) connects with Kami Pullakhandam, a clinical trials navigator.

First Lady Jill Biden Visits as Part of Cancer Moonshot

First lady Jill Biden, EdD, met with top UCSF cancer officials in October to hear about progress on the National Cancer Moonshot and to mark Breast Cancer Awareness Month.

Hosted by Alan Ashworth, PhD, president of the UCSF Helen Diller Family Comprehensive Cancer Center and the E. Dixon Heise Distinguished Professor of Oncology, the first lady heard about the complexities of cancer, as well as UCSF advances in breast cancer research and programs that support breast cancer patients, survivors, and caregivers.

As part of the visit, Laura Esserman, MD, MBA, director of UCSF's Breast Care Center, discussed two landmark national clinical stud-

ies she's leading – the I-SPY2 Trial and the WISDOM study – that aim to better understand breast cancer and to reduce the toll of the disease. “We don't think [care] is one-size-fits-all,” said Esserman, the Alfred A. de Lorimier Professor of General Surgery. “We want to screen smarter: less for those who don't need it and more for those who do. Every woman from every community deserves a chance to participate.”

Jill Biden came to UCSF in 2016 with then-Vice President Joe Biden as part of the launch of the Cancer Moonshot, which aimed to accelerate progress against cancer; the initiative was rekindled by President Biden in early 2022.

Reprogramming the Brain's Cleaning Crew

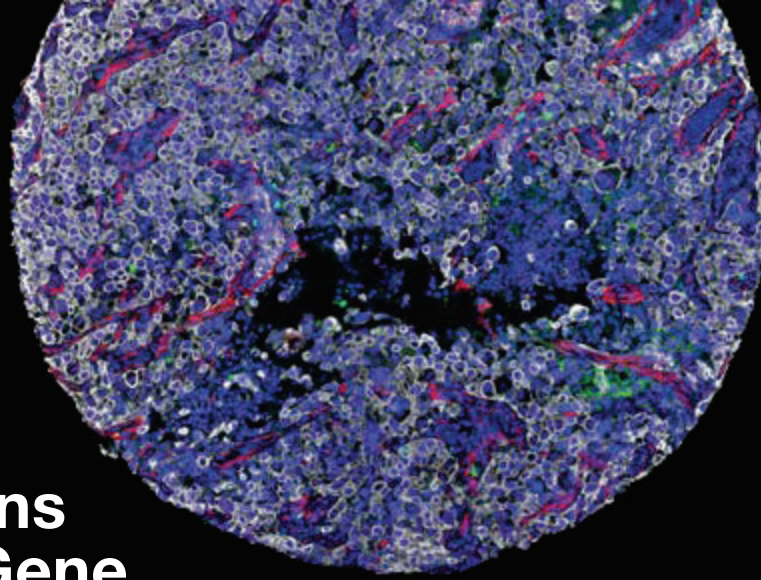
A recent UCSF discovery – how to shift damaged brain cells from a diseased state back to a healthy one – presents a potential new path to treating Alzheimer's disease and other forms of dementia.

The research focuses on microglia, cells that stabilize the brain by clearing out damaged neurons and the protein plaques often associated with dementia and other brain diseases.

These cells are understudied, despite the fact that changes in them are known to play a significant role in brain diseases, says Martin Kampmann, PhD, senior author of the study.

“Using a new CRISPR method we developed, we can uncover how to actually control these microglia, to get them to stop doing toxic things and go back to carrying out their vitally important cleaning jobs,” says Kampmann, an associate professor at the UCSF Weill Institute for Neurosciences. “This capability presents the opportunity for an entirely new type of therapeutic approach.”





Microscopy of a lung tumor biopsy

Drug Turns Cancer Gene Into ‘Eat Me’ Flag for Immune System

Tumor cells are notoriously good at evading the human immune system; they put up physical walls, wear disguises, and handcuff the immune system with molecular tricks. Now, UCSF researchers have developed a drug that overcomes some of these barriers by marking cancer cells for destruction by the immune system.

The new drug, described in *Cancer Cell*, pulls a mutated version of the protein KRAS to the surface of cancer cells, where the drug-KRAS complex acts as an “eat me” flag. Then an immunotherapeutic agent can coax the immune system to effectively eliminate all cells bearing this flag.

“The immune system already has the potential to recognize mutated KRAS, but it usually can’t find it very well. When we put this marker on the protein, it becomes much easier for the immune system,” says Kevan Shokat, PhD, who helped lead the new work. Shokat is a professor and chair of cellular and molecular pharmacology and a Howard Hughes Medical Institute investigator.

KRAS mutations are found in about one-quarter of all tumors, making them one of the most common gene mutations in cancer. Mutated KRAS is also the target of another new drug, which just received preliminary approval from the Food and Drug Administration for use against lung cancer, and the two approaches may eventually work well in combination.

Molecules Squelch Pain Without Sedation



A newly identified set of molecules alleviated pain in mice while avoiding the sedating effect of opiates, according to a new UCSF-led study. The molecules act on the same receptor as clonidine and dexmedetomidine – drugs commonly used in hospitals as sedatives – but are chemically unrelated to

them and may not be addictive. Clonidine and dexmedetomidine are effective painkillers but have such a sedating effect that they are rarely used for pain relief outside of hospitals. The new compounds are strong candidates for painkilling alternatives to narcotics, say the researchers.

Recommended: Books, Videos, & Podcasts



READ

The Sleep Prescription

Drawing on his experience as a sleep scientist at UCSF, Aric Prather, PhD, a professor of psychiatry and behavioral sciences, shares his simple but powerful seven-day plan to achieve restorative rest.



WATCH

2022 UCSF Medals: The Black Caucus, Jennie Chin Hansen, David Julius

UCSF bestowed its highest honor on three co-founders of the Black Caucus who fought for racial equality, a nurse and alum who led systemic change in senior health care, and a scientist awarded a 2021 Nobel Prize. Find on UCSF’s YouTube channel.



LISTEN

Revolutionary Care: An Oakland Story

Oakland has a long history of leading the way in treating sickle cell disease, from the 1970s’ Black Panthers health clinics to a new gene therapy using Nobel Prize-winning science. This new podcast explores the saga’s rich past and promising future. Find on your favorite podcast forum.

How Much Can We Control Our Own Fertility?

People trying to conceive are bombarded with advice meant to improve their odds. But how much power do we really have over our fertility?

By Christina Hernandez Sherwood

Nearly one in five American women experience infertility, meaning they're unable to become pregnant after at least a year of trying to conceive, or six months if they're age 35 or older.

Should they cut the caffeine? Or take up yoga to de-stress? An infertility diagnosis can lead some hopeful parents to search for ways to boost their odds of getting pregnant. But despite the medical advances of recent decades, it's not always possible to improve on our basic biology.

We asked UCSF fertility experts what we *should* focus on – and what's beyond our control.

MYTH # 1: If I'm healthy and fit, then my age doesn't matter to my fertility.

Unfortunately, this myth is false.

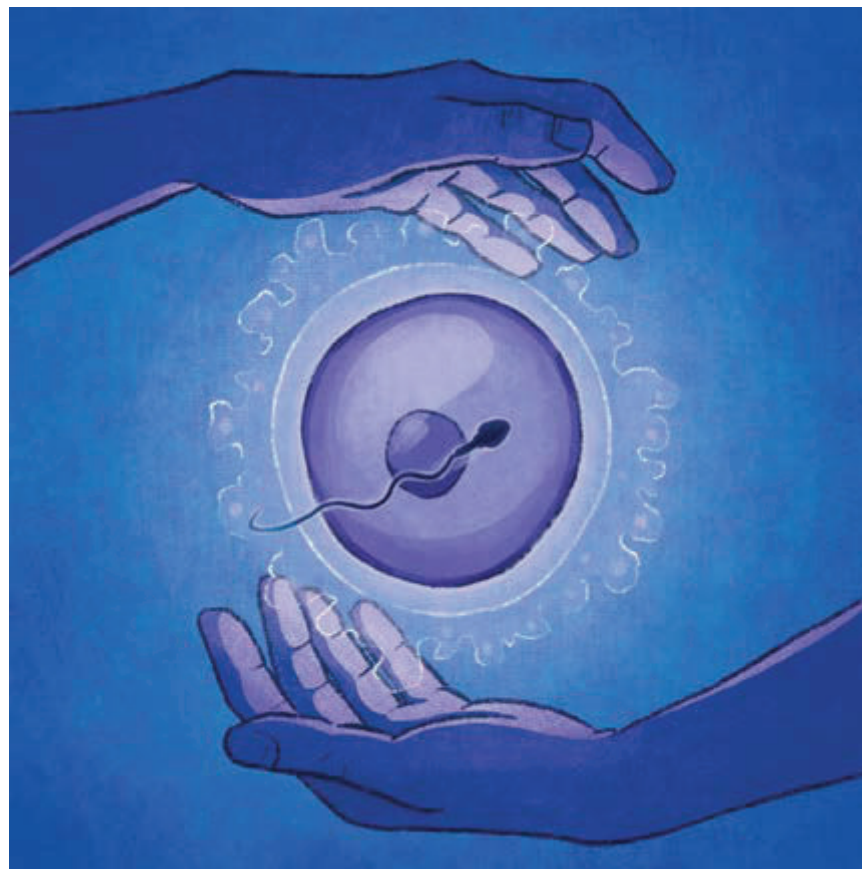
Age is the most important driver of a woman's fertility, says Marcelle Cedars, MD, who directs UCSF's Division of Reproductive Endocrinology and Infertility. "The ovary," she says, "seems to have its own clock."

Aside from major health risk factors, such as obesity or drug use, the general health of someone who's trying to conceive has little bearing on their eggs' quality – that is, an egg's ability to be fertilized and create a viable embryo.

Eggs begin to age from the moment a person is born, so a 40-year-old will have four-decade-old eggs, even if they exercise enough to have the cardiovascular fitness of someone half their age. By age 42, some 80% of an individual's remaining eggs are considered abnormal.

"It's kind of our modern tragedy," says Diana Laird, PhD, a professor of obstetrics, gynecology, and reproductive sciences whose research at UCSF focuses on aging and sex cells of laboratory mice. "The ovary is the first organ that appreciably and functionally ages."

Yet many of the chromosomal abnormalities in an individual's eggs are present before they are even born. "An egg starts growing when you're only about four weeks old in the womb," Laird says. "This is an incredibly long and complex process that ends with the ovulation of that egg at whatever age you are."



Her research seeks to untangle how much of an egg's decline is related to the years it sits in "suspended animation" and how much was preordained by events that happened decades before during the egg's development.

"How do we identify eggs that had a healthier development process," Laird says, "and are more likely to give us a healthier egg and a healthier baby?"

MYTH # 2: I caused my own infertility because I'm too stressed out.

"Relax and you'll get pregnant!" While perhaps well intentioned, this advice is just plain wrong – as two UCSF studies, conducted a decade apart and on different aspects of the conception process, proved in both humans and mice.

Women who reported feelings of psychological distress before in vitro fertilization (IVF) treatment were just as likely to become pregnant as those who claimed to be stress-free, wrote Lauri Pasch, PhD, a UCSF psychologist who specializes in infertility, in a 2012 article in the journal *Fertility and Sterility*. In fact, rather than stress causing fertility problems, Pasch found that IVF failure was often followed by subsequent distress.

Just how stressful is an infertility diagnosis? Both Cedars and Laird noted an eye-opening finding from a 1993 study: People with infertility were as anxious and depressed as those with a cancer diagnosis.

But luckily, even egg and sperm precursors developing in embryos inside pregnant mice can't sense stress during development, according to a forthcoming paper from Laird's lab. Although these precursors contain receptor proteins with the ability to sense the stress hormone cortisol, Laird's team found that they were unable to sense stress hormones at that stage of development.

"They insulate themselves from stress in their environment," Laird says of the egg and sperm precursors. "The news is good for expectant patients."

So from before a parent's birth through the post-conception period, the research remains consistent: "There are no data to say that stress causes infertility," Cedars says.

MYTH # 3: If I undergo IVF, I'll go into menopause earlier.

Twenty eggs retrieved in an IVF cycle means 20 fewer ovulation cycles in a woman's lifetime, right? No, Cedars says.

Before an IVF treatment, fertility doctors often prescribe hormonal injections intended to stimulate a patient's ovaries to produce a larger number of mature eggs. (The more eggs retrieved, the better the chances are that at least one will result in a normal embryo.)

But these "extra" eggs aren't hijacked from a person's future ovulation cycles. Instead, they are eggs that would have died during the current cycle without ever reaching maturity.

The ovaries contain a so-called "resting pool," from which a cohort of eggs departs each month – let's say 20 eggs. In a typical ovulation cycle, only one of those 20 eggs will mature. The other 19 will die and be reabsorbed into the body. (Just 0.1% of the eggs in a person's body will mature and be ovulated during their lifetime.)

But pre-IVF hormonal stimulation could result in all 20 eggs from a single cohort potentially reaching maturity. These aren't eggs that would have matured and ovulated in later cycles. Rather, they would have perished but instead were "rescued" by the medication.

Conversely, Cedars adds, eggs aren't "saved up" when a person is not ovulating, such as when ovulation is suppressed by birth control. Birth

control only blocks the single egg that would have ovulated from reaching maturity – but the process of eggs leaving the resting pool still happens.

"You don't preserve or protect eggs," Cedars says, "just because you're not ovulating."

MYTH # 4: Infertility is a women's issue.

Sure, but it's also a men's issue. In up to half of all cases of infertility, Cedars says, the male partner is the sole or a contributing factor.

As with the mother, the age of the father can play a role in reproductive health, Laird says. Spermatogonial stem cells churn out sperm continuously throughout a man's lifetime. But with each additional year of a father's age, his sperm passes about two additional genetic mutations on to his child, though most of these mutations aren't consequential.

Even so, infertility is often characterized as a women's issue. After all, it is the individual with the uterus who becomes pregnant and who, most often, undergoes fertility treatments – taking medications or having procedures – even if the other partner's sperm is the sole factor in the infertility.

Historically, patients with infertility were treated by gynecologists and reproductive endocrinologists. Male partners were the purview of urologists, who are primarily surgeons. But not much in male infertility requires surgical treatment.

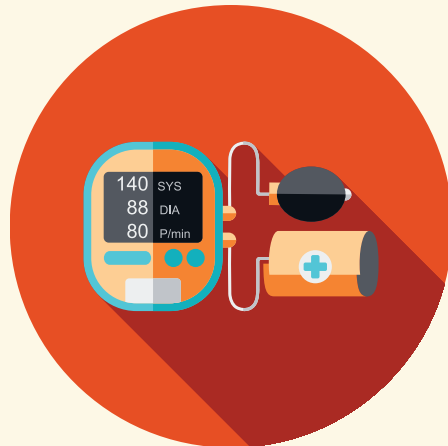
"Male-fertility specialists are decades behind where we are caring for women," Cedars says, "because it wasn't even a specialty in the past."

Today, male-reproductive specialists are more prevalent. UCSF has a male-reproductive health team, within the Department of Urology, that offers male-fertility preservation counseling and treatment, evaluation and treatment for male reproductive health problems, and other services.

"It's an exciting time for the field of male fertility due to the increasing interest," Cedars says, "and the importance of genetics in male reproductive health."

Marcelle Cedars is the Laura Ambroseno and Raffaele Savi Family Presidential Chair of Reproductive Health.

Basics May Be Best for Home BP Checks



When patients are diagnosed with hypertension – as nearly half of American adults have been – they are often advised to buy a blood pressure monitoring device to use at home. Daily home readings paint a clearer picture of a patient's blood pressure than those taken only every few months at the doctor's office.

A new, national study led by UCSF investigated whether newer monitoring devices that pair with smartphones result in better management of hypertension than home blood pressure cuffs. To their surprise, the researchers found that the more sophisticated devices don't lead to better blood pressure control. They say the findings provide practical, real-world answers for doctors and patients.

Breakthroughs and Other Buzz

Like LSD but no trip:

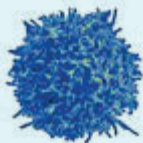
A team of scientists from several universities, including UCSF, has designed compounds that hit the same receptor that LSD activates, but without causing hallucinations. A single dose in mice produced powerful antidepressant and anti-anxiety effects that lasted up to two weeks.

Autism and moms' depression:

About half of moms of kids with autism spectrum disorders have higher levels of depressive symptoms than mothers of neurotypical children, according to UCSF research. The good news: The depression did not worsen children's behavior problems over time.

Long COVID got you winded?

Brain fog, fatigue, headache, and now this? A new UCSF study points to another persistent effect of COVID, identified months after infection: reduced exercise capacity.



Bolstering tired T cells

T cells used in immunotherapy can get exhausted from fighting cancer cells, or even shut down as they enter tumors, but an edit using CRISPR helps build up their strength, a UCSF and Gladstone Institutes study found.

Vascular cell secrets:

UCSF scientists have finally shown how blood vessel cells develop in the prenatal human brain, paving the way to fully understanding the role of these cells in healthy brain development and disease.

Post-sex antibiotic for STIs: Incidence of chlamydia, syphilis, and gonorrhea has soared over the past two decades, but a single dose of doxycycline, a widely used, cheap antibiotic, reduced the risk of all three sexually transmitted infections, a UCSF investigation showed. Chlamydia and gonorrhea risk dropped by over 60%.

Beware tweens and screens:

Tweens who spend more time on screens have a higher likelihood of developing disruptive behavior disorders, found a UCSF-led study, with social media having an especially strong influence.



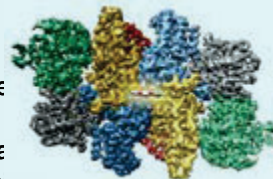
Cancer risk from common products: Pregnant women in the U.S. are exposed to cancer-causing chemicals in dishware, hair coloring, plastics, and other common products, according to research from UCSF and Johns Hopkins Bloomberg School of Public Health. The chemicals are not regularly monitored.



Health impact of kids' neighborhoods:

Children living in neighborhoods with greater hardships, such as substandard housing, are more likely to use emergency departments, including for complaints that could be managed by their pediatricians, found a study led by UCSF Benioff Children's Hospitals.

Reversing effects of concussion: A small molecule called ISRIB that was identified at UCSF can reverse the neuronal and cognitive effects of concussion in mice weeks after an injury occurred, UCSF research found.



Freeing up anesthesiologists:

Ophthalmologists may be able to safely cut back on having anesthesiologists or nurse anesthetists routinely present during cataract surgery, according to a UCSF study. This would help ease a shortage of these specialists.

Your heart on marijuana:

A UCSF study of 23 million people found that use of marijuana, meth, cocaine, or opiates is linked to atrial fibrillation, a potentially lethal heart disorder.



Uneven grip of loneliness:

The pandemic led to loneliness for many of us. Research from UCSF and Northwestern found it hit low-income and Hispanic/Latinx people especially hard.

Shock to the system:

Becoming homeless later in life leads to a "health shock," say UCSF researchers, who found that older adults are more likely to die than younger people who lose housing.

Eyeing our dreams:

UCSF scientists discovered that when our eyes move during deep sleep, we're gazing at things in the dream world our brains have created. The findings shed light not only on how we dream but also on how our imaginations work.



Video games for aging brains:

After a decade of work, scientists at UCSF have developed video games that improve key aspects of cognition in aging adults, such as attention and short- and long-term memory.

Time to step it up?

Physical activity decreased during COVID and still hasn't rebounded, a UCSF analysis of step counts revealed.

The Case of the Suspicious Swelling

A grandmother showed telltale signs of a common endocrine disorder. But a puzzling lab result put the detective skills of physicians Joan Addington-White and Rob Weber to the test.

By Jill Sakai



A WOMAN IN HER MID-50s ARRIVED at an outpatient clinic at Zuckerberg San Francisco General Hospital complaining of swelling in her legs. “When I walked in the room, I realized I had seen her before,” says Joan Addington-White, MD, the physician on call.

The patient had visited the clinic a number of times before. But this time, she looked strikingly different, thought Addington-White, who is a UCSF professor of medicine and the residency director of the hospital’s primary care internal medicine training program. The patient showed her a year-old photo on her phone that confirmed Addington-White’s memory: She had been much thinner and strong enough to stand and hold her 2-year-old grandchild. Now, her whole body was swollen, and she needed a wheelchair to get around.

Upon conducting a careful physical exam, Addington-White noted high blood pressure, a rounded face, new body hair growth, a fat deposit on the patient’s upper back, abdominal stretch marks, and thin – almost translucent –

skin. This constellation of symptoms is characteristic of Cushing’s syndrome, an endocrine disorder caused by excess levels of steroid hormones such as cortisol – often due to an adrenal or pituitary tumor or the long-term use of steroid medications.

Addington-White called on Rob Weber, MD ’19, PhD ’17, then a resident in internal medicine, to admit the patient to the hospital, confirm her steroid levels, and track down their source. The medical team asked about her current medications and supplements, but the list she gave didn’t include any steroids. And when they tested her cortisol levels that night and again in the morning, the results shocked them. “Her cortisol was *zero*,” Weber says. “That didn’t make sense.”

Then came an unexpected clue: The patient complained of shoulder pain and asked for some pills she had at home but hadn’t mentioned before. Weber’s ears perked up, and he asked the woman to elaborate. Since tearing her rotator cuff a year earlier, she said, she’d been taking an unregulated

arthritis supplement from Mexico. Weber’s team asked her family to bring the pills in so they could examine them.

The bottle’s ingredient list was fairly benign: vitamins, collagen, glucosamine, curcumin. But an online search turned up articles in Spanish warning that the supplement often contained unlabeled ingredients, including steroids. Sure enough, an analysis revealed the pills contained high doses of dexamethasone, a synthetic steroid. Weber’s team also found dexamethasone in the woman’s blood; the drug can suppress the body’s cortisol production, explaining why her supply was nil.

But abruptly stopping a high-dose steroid can send the body into shock, so the team prescribed a tapering regimen. Although Cushing’s syndrome is typically reversible, the woman’s ongoing treatment is complicated by additional health problems, including severe degeneration of her shoulder and hips – likely caused by the high-dose steroids. She is on the road to recovery, her doctors hope, though it may be a bumpy one.

Mission: A **Tobacco-Free** World

Youth smoking rates in the U.S. were at all-time lows when flavored e-cigarettes hit the market 15 years ago, sparking an epidemic of novel nicotine products. Also called vape pens, these devices heat up liquid that contains nicotine and other chemicals, creating an aerosol that's inhaled.

Pamela Ling, MD '96, MPH, applies her research-driven social media and marketing expertise to beat the tobacco industry at its own game – and avoid similar pitfalls with cannabis.

By Janet Wells

In the 1950s, 45% of the U.S. adult population smoked. By 2020, that figure was down to 12.5%. Is tobacco still a public health crisis?

Tobacco remains the leading preventable cause of disability and death in this country, responsible for 1 in 5 deaths – 480,000 people a year.

It's great news that smoking rates are continuing to come down. But e-cigarettes are slowing progress. Vaping is harmful and has taken over the youth market. In California, five times more young people vape than smoke cigarettes.

The U.S. Food and Drug Administration (FDA) only started regulating cigarettes and smokeless tobacco in 2009. It was another seven years before they began regulating e-cigarettes. During this time, the industry was selling fast and furiously, even coining the term “vape” to get away from negative associations with cigarettes.

Right now, young people's use of tobacco products is a driving concern. A lot of youths who were not addicted to cigarettes started vaping – largely due to unfettered availability and marketing. In 2021, 2% of high school students nationally smoked cigarettes, but more than 11% vaped.

Juul Labs recently agreed to pay \$440 million to settle an investigation by nearly three dozen states into its sales tactics to youths. Will that have an impact?

The settlement put some limits on advertising, but it only applies to Juul, which has already lost a huge percentage of the market share after bowing to pressure to drop fruit flavors. Juul look-alike brands immediately took over that niche.

So how do we get kids to stop vaping, or even better to never start?

Early in my career, I got interested in tobacco and marketing to learn how the industry convinced young people to do something that kills them. I use those strategies to improve smoking prevention and cessation by making the advice relevant and accessible to the people we're trying to reach. For example, to address teenage vaping, we adapted the look and mes-

saging of a smoking-cessation group-support program UCSF developed on Facebook and put it on Instagram because teenagers are not on Facebook anymore.

There's been a lot of talk about vaping's potential benefits – like Juul's claim that it helps people quit smoking cigarettes. Is there science behind that?

The evidence is still in its infancy. For smoking cessation, a few studies found e-cigarettes were as effective as other nicotine replacements in controlled situations. But the reality is that most people who vape also continue smoking cigarettes, and most revert back. If someone wants to quit smoking by vaping, we have to try to mimic the situation you get in a randomized trial with close supervision and structured plans to quit. Switching on your own, going to the corner store to buy your vape products, not having any counseling support – that depresses quitting.

There's also some indication that smokers who switch completely to e-cigarettes reduce their exposure to toxins, but we don't know if that reduces meaningful outcomes like heart attacks. Some use this data to claim vaping is “safer” than smoking – but almost anything is.

What trends are you watching?

New marketing of old nicotine-cessation products for recreational use – like pomegranate-flavored gum or lozenges. Also, the expansion of vitamin vapes – B12, melatonin, CBD, aromatherapy – marketed in cute packaging as a “healthy” way to reduce stress, suppress appetite, or get antioxidants. There's no evidence of any health benefit, and they may be dangerous – they're still putting heated aerosols into the lungs. Because these products don't have nicotine or psychoactive THC, they're classified as supplements, with very little regulation. You can buy them at places like Urban Outfitters.

A tobacco-free world is the center's mission. Is that within reach?

We're quite hopeful that it is, particularly in California, where the smoking rate is at a historic low – about 10%. The challenge is that

smoking is now concentrated in marginalized groups, like communities of color and people with mental health and substance abuse issues. These populations are targeted by industry. We're working cooperatively with people in high-risk communities to address disparities and find solutions. Take African American smokers – 80% use menthol products. In 2020, California banned the sale of menthol and other flavored tobacco products. The industry spent millions trying to defeat the policy in a ballot initiative – but luckily in November 2022 voters upheld it.

Now that recreational cannabis use is legal in 19 states, there's a proliferation of products. Are these good, bad, or somewhere in between?

The research is very slow to progress. With the history of medical marijuana use, especially in California, people perceive cannabis to be safe and therapeutic. I've had study participants say, “Secondhand cigarette smoke will kill you, but secondhand marijuana smoke, that's medicine.” It's not. Cannabis smoke has been shown to have cardiovascular effects similar to cigarette smoke.

There are clear evidence-based applications, such as the use of cannabinoids for nausea caused by chemotherapy. But claims that these products manage depression, anxiety, sleep, and a host of “wellness” benefits are not supported by research. Cannabis can be used legally, but we need to beware of marketing hype. There's also growing concern about the packaging of edibles – mimicking Sour Patch Kids candy or Oreo cookies – connected to poisoning of kids.

We need to look at lessons learned from tobacco control and apply them to cannabis. Even basic things like visible warning labels and childproof packaging. We got rid of candy-flavored cigarettes over a decade ago. As we're looking at the end of the tobacco epidemic, we need to avoid the dawn of a commercialized cannabis public health disaster.

Pamela Ling is the American Legacy Foundation Distinguished Professor of Tobacco Control and director of the UCSF Center for Tobacco Control Research and Education.



The title 'TRIP THERAPY' is rendered in a large, bubbly, rounded font. The letters transition in color from a reddish-pink on the left to a deep purple on the right. To the left of the word 'TRIP' is a stylized illustration of a mushroom with a red cap and a thin stem. To the right of 'TRIP' is another stylized mushroom with a blue cap and a thin stem. The word 'THERAPY' is positioned directly below 'TRIP' in the same font and color gradient.

TRIP THERAPY

COULD PSYCHEDELICS BECOME MAINSTREAM M E D I C I N E S ?

By Lexi Pandell
Illustrations by Marcos Chin

When Tom Solis, a renowned chef and baker, fell ill with AIDS in the 1990s, he believed he would soon die. But breakthrough drugs called protease inhibitors quickly put him back on a path to a fairly normal life. Still, he struggled for years with the challenges of managing his disease and the deaths of loved ones in his community. “I felt I always had this tight armor that I could not get out of,” he says.

Then, in 2016, a doctor suggested he look into a clinical trial at UC San Francisco that had just begun recruiting patients for a study of psychedelic therapy in long-term AIDS survivors experiencing demoralization, a kind of existential distress. Solis jumped at the chance. “I’ll be totally honest,” he says. “I wanted to get super-high.”

And that he did. The experience was also one of the most profound of his life. It was momentous for UCSF, too, because the trial marked the beginning of the University’s

foray into the fast-growing field of psychedelic medicine.

In 1970, when the U.S. Drug Enforcement Administration (DEA) categorized psychedelics like psilocybin and LSD as Schedule I drugs – the most highly regulated substances – academic studies of them all but ceased. But now, after decades of being pushed to the fringes, research into the healing powers of psychedelics is undergoing a renaissance. In preliminary trials, researchers at UCSF and other institutions around the world are finding that these once-villainized substances show promise in treating a remarkably wide range of mental health disorders, including post-traumatic stress disorder, depression, and addiction.

And for some early trial participants, such as Solis, the drugs’ curative effects have lingered long after the studies concluded.

Down the Rabbit Hole

The impetus for UCSF's first psychedelic medicine trial wasn't, as might be suspected, Burning Man – an annual art festival in the Nevada desert known for encouraging radical ideas and hallucinogen use – but a San Francisco mansion with an unobstructed view of the Golden Gate Bridge. It was the home of George Sarlo, a venture capitalist and philanthropist. In 2015, Sarlo hosted a dinner for students and facilitators who had participated in undergraduate psychology training he had funded. Among the guests was a young UCSF psychiatrist and researcher named Joshua Woolley, MD '07, PhD '05.

Woolley, a self-described square with an earnest, chatty energy, listened as Sarlo regaled the group with a tale of taking ayahuasca, a drink brewed from a bark that contains a psychedelic known as DMT, which causes intense hallucinations. Anyone who has chatted with a “psychonaut,” as devotees of psychedelics are known, knows that trip stories can be as meandering and convoluted as people's dreams. But Woolley was captivated.

Sarlo had grown up in Budapest and had survived the Holocaust. His father had disappeared one day into a work camp and never returned. It wasn't until he took ayahuasca, Sarlo said, that he was finally able to confront his past. He described seeing a vision of dead bodies in the snow, including a skeleton he knew was his father. He asked the skeleton why he had never said goodbye; his father responded that he'd thought he would return and added, “With my last breath, I blessed you and I promised to guard you all your life.”

At the time, Woolley's lab at UCSF was investigating whether oxytocin – a hormone known as the “love drug” – could facilitate group therapy for methamphetamine addicts. “You're giving this drug with the idea that you could change social behavior – and maybe trust, openness, and emotional responses – to make the therapy more effective,” he says. Psychedelics, which have similar mind-opening effects, had been on his radar, but he'd never tried them himself and hadn't imagined he would be the type to study them.

As he listened to Sarlo enthuse about their virtues, he thought “Why not?” He had a lab at a world-class biomedical institution and was familiar with running clinical trials. The only problem? “Few researchers at UCSF had any expertise in psychedelic trials, so it was kind of the Wild West,” Woolley says. He did, however, know someone who could help.

Brian Anderson, MD, MSc, at the time a UCSF resident in psychiatry, had studied the serotonin system, a neurotransmitter network in the brain that psychedelics act on, and had earned a master's degree researching Brazilian churches that use ayahuasca for spiritual practices. Like Woolley, he had assumed that pursuing psychedelic medicine trials was not, as he politely puts it, “something that would be beneficial for your academic career.” But he was keen to contribute to the effort and signed on to lead the first trial.

Woolley (now an associate professor) and Anderson (an assistant professor) also recruited Jennifer Mitchell, PhD '99, a professor of neurology and of psychiatry and behavioral sciences, who was interested in exploring the therapeutic benefits of MDMA, a psychedelic commonly known as “ecstasy” or “molly.” But the team soon encountered another roadblock: Nobody wants to take mind-altering hallucinogens in a sterile hospital room.

What the psychedelic community calls “set and setting” – that is, a person's mindset when they trip (the “set”) and their environment (the “setting”) – has a profound effect on their experience and on the drug's long-term effects. Taking psychedelics in a forest, for example, is different from taking them at a music festival, and both of those are different from taking them in a quiet room in the presence of two professional, sober facilitators. “You need a room that you can decorate, have a couch in, play music,” Woolley says. “That's not easy to do at a university.”

The researchers also needed the DEA's permission to use Schedule I substances, an arduous process that involved an investigation of the spaces they intended to use for the study. But for-

tuitously, as Anderson sniffed out, UCSF already had a Schedule I-approved drug safe in its investigational pharmacy. And in UCSF's Langley Porter Psychiatric Hospital, there was an empty research suite that had previously been used to test the side effects of Schedule I drugs. The team decorated it with art, a patterned rug, a sofa bed, and lamps that cast a soft light.

For the trial, they chose to focus on demoralization among long-term AIDS survivors, a decision that resonated with UCSF's history as ground zero for treating patients during the AIDS crisis. Facilitators would give participants a standardized dose of psilocybin, the active ingredient in so-called “magic mushrooms.” The dose would be high enough to put them into a dreamlike state, but they likely wouldn't lose touch with reality. Following their trips, the participants would meet for group therapy sessions to process their experiences.

“A lot of the men had struggled with social isolation,” Anderson says. The goal of the group therapy, he explains, was to help them “connect with each other and find support with each other.” Ultimately, the team hoped, this psychedelics-plus-therapy regimen would allow these men to break free of the stigma, depression, and loneliness they'd carried with them for so long.

By 2017 – with funding from Sarlo and others, including the Usona Institute and the Heffter Research Institute – the study began.

New Perspectives

Indigenous cultures have used naturally occurring psychedelics – such as ayahuasca, psilocybin (which can be found in more than 180 species of mushrooms), and peyote (a cactus that contains mescaline) – for millennia. They take these drugs “not just to treat mental illness,” Anderson says, “but for forms of prayer, to facilitate community gatherings, to solve community and personal issues, and to address all sorts of challenges to human flourishing.” In the 1950s, after chemists had isolated and synthesized several psychedelic compounds in the lab, Western researchers began studying their effects on a plethora of health conditions, including addiction, anxiety, schizophrenia, end-of-life pain, and depression. More than 1,000 studies were published on LSD-enhanced psychotherapy alone.

But in 1970, after the Controlled Substances Act put hallucinogens in the Schedule I category,

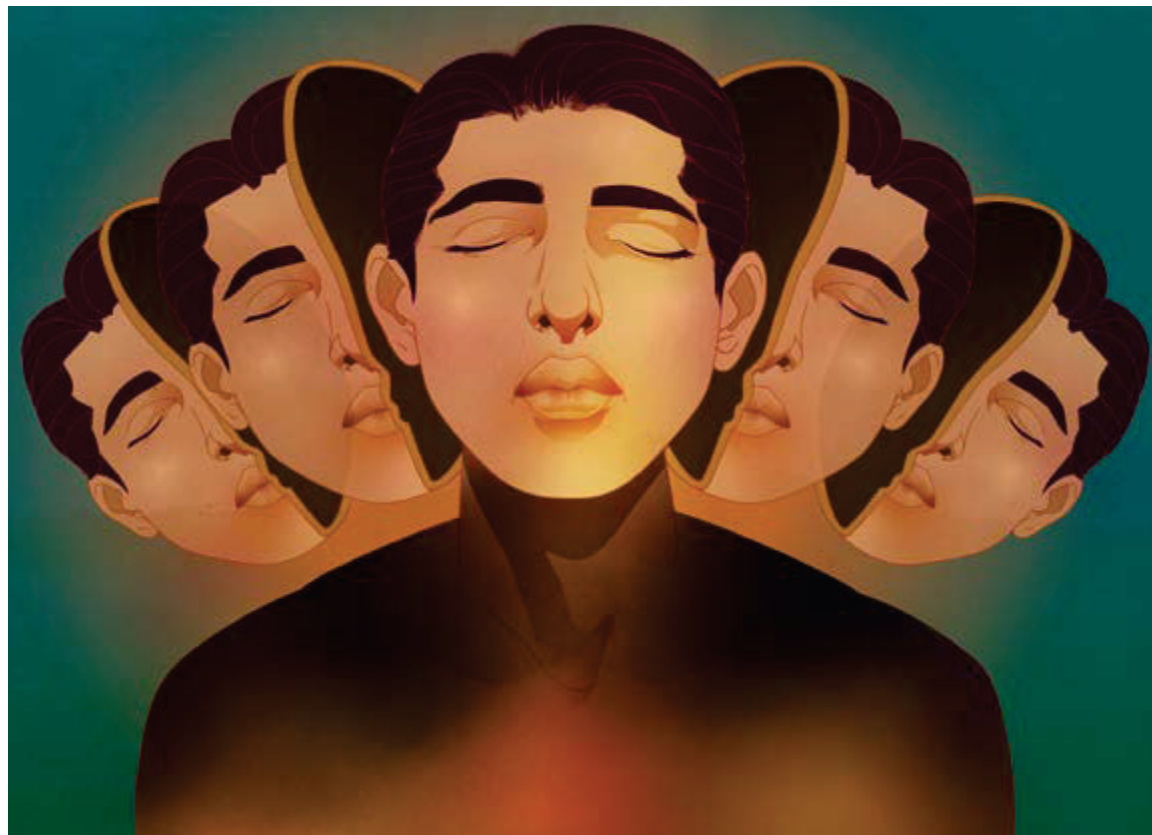


many of the early pioneers in the field turned away from studying psychedelic therapies for fear of stigmatization or of losing their medical licenses – or simply to avoid the many impractical and burdensome regulatory hurdles. The drought in psychedelics research lasted for more than 30 years until, in 2006, a breakthrough was announced. Researchers at Johns Hopkins University had managed to get permission from the DEA and the U.S. Food and Drug Administration (FDA) to study psilocybin and had published a paper showing that the drug brought on mystical experiences in healthy volunteers. The study provided a road map for other scientists itching to enter the field, and soon, institutions across the country were once again embracing psychedelics as promising therapeutic agents.

Psychedelics seem to help patients break down personal barriers and access new perspectives. (See “How do psychedelics work?” on page 19.) “Often, the experience can be blissful,” Woolley says. “However, sometimes it can be very challenging and open up people to memories and feelings they did not expect.” Psychedelics tend to amplify emotions, positive or negative. “Patients encounter their psyches, their own fears, and their own strengths as well,” says Gisele Fernandes-Osterhold, MA, a licensed psychotherapist who works with Woolley as the director of facilitation for several psychedelic therapy trials now underway at UCSF.

This was the case for Tom Solis, the AIDS survivor. Before joining the initial UCSF trial, he had experimented with psychedelics, but he’d never taken as high a dose as the study prescribed. In the trial, after swallowing a psilocybin capsule, he slipped on an eye mask and headphones playing instrumental music.

As the drug took effect, he says, “I went deeper and deeper and deeper.” A vision of one of his three brothers came to him. His brother’s face was in profile, like a face on a coin. The image was clear and compelling; Solis had been close with this brother growing up. Another brother



“I FELT THIS GREAT RELEASE IN MOVEMENT BECAUSE I HAD THE FREEDOM TO DO IT NOW. I WAS UNENCUMBERED. I WAS PURE.” –Tom Solis

appeared more faintly; Solis had a more complicated relationship with this one. And then the third brother, with whom Solis had the weakest connection, appeared dimmest of all.

To Solis, the three apparitions “represented the familial, cultural judgment – that no matter what I did, it wasn’t good enough.” The brothers vanished, and suddenly, Solis was overcome with a new thought: *I am worthy; you guys are wrong. You don’t realize what you’re missing.*

The defensive armor that he’d always felt vanished, too. “It was just like a sugar coating that melted in the rain,” he says. “It was that quick.” Solis realized he could break the cycle of rejection by being present for his brothers in a way they hadn’t been there for him. He then began to move through some yoga poses. “I was on the bed, dancing,” he recalls. “I felt this great release in movement because I had the freedom to do it now. I was unencumbered. I was pure.”

Not every participant in the first UCSF trial had such an ecstatic experience. Of the 18 participants, four reported that they felt paranoia during their trip. One, who had never become ill from HIV, suffered severe nausea and hallucinations of vomiting and soiling himself. He later said that the trip was nonetheless meaningful: He believed the hallucinations reflected his intention to better understand the experiences of loved ones who had died of AIDS. (Research so far suggests that both good and bad trips can lead to positive outcomes.)

Overall, participants largely reported decreased feelings of existential distress, better mood, and less anxiety – which lasted weeks to months after their trips. The trial ended in early 2019, and the results were published in October 2020 in the Lancet journal *eClinicalMedicine*.

ILLUSTRATIONS: MARCOS CHIN

Trial Fever

Psychedelics research is now booming. Journalist Michael Pollan's bestselling 2018 book, *How to Change Your Mind*, brought mainstream attention to psychedelic therapy. And as foundations and pharmaceutical companies took note of the excitement, funding for clinical studies began flowing more readily.

Bolstered by the success of the psilocybin trial in AIDS survivors, UCSF researchers began investigating psychedelics for a variety of disorders. Woolley launched the Translational Psychedelic Research (TrPR, pronounced "tripper") Program, a consortium of UCSF researchers that is now investigating psilocybin as a treatment for eating disorders, for depression in people with bipolar disorder, and even for chronic low back pain. Because so much of pain is about perception, the researchers hypothesize, psychedelics might help patients learn to manage their pain with less emotional suffering.

In collaboration with the UCSF Movement Disorders Center, TrPR is also testing psilocybin for depression and anxiety in Parkinson's patients – the first-ever trial in the U.S. to use a psychedelic for a neurodegenerative disorder. Previous studies suggest that psilocybin and LSD create long-term changes in cognitive function and coping strategies. They may also enhance the brain's ability to acquire new information and make new connections, functions that are often impaired by depression and other neuropsychiatric disorders. For this reason, researchers believe these drugs could be most useful for treating conditions related to existential distress, addiction, or being stuck in certain ways of thinking.

The decision to study Parkinson's – a degenerative brain disorder marked by uncontrollable movements, loss of coordination, and difficulty with balance – may seem puzzling. But "Parkinson's is like an iceberg," says Ellen Bradley, MD, who is leading the trial, which will end early this year. "Motor features are above the water, but there's this giant part that's invisible but impactful for functioning." Depression and anxiety, in particular, plague many people with Parkinson's, but such patients don't tend to respond well to antidepressant or anti-anxiety medications.

Because this trial involves a neurological disorder, Bradley's team has taken extra safety precautions, including screening for comorbidities, such as dementia, and giving patients a lower initial dose of psilocybin. "You want to tar-



PSYCHEDELICS SEEM TO HELP PATIENTS BREAK DOWN PERSONAL BARRIERS AND ACCESS NEW PERSPECTIVES.

get certain symptoms, but it won't be a useful real-world treatment if it makes other parts of the illness worse," explains Bradley, who is an assistant professor of psychiatry and TrPR's associate director.

In 2021, UCSF launched a Psychedelics Division within its Neuroscape translational neuroscience center and recruited Robin Carhart-Harris, PhD, to head it. Carhart-Harris, the Ralph Metzner Distinguished Professor, is known for studying the brain activity of people on psychedelics and has become something of a rock star in the world of psychedelics science. Under his leadership, Neuroscape researchers are planning clinical trials of psilocybin for end-of-life distress and alcoholism. And Jennifer Mitchell, now a member of the group, is leading two phase III trials of MDMA for post-traumatic stress disorder, the final step to earn FDA approval for its use in clinical settings. MDMA, which stimulates the release of oxytocin, as well as the hormones cortisol and vasopressin, seems to help patients confront and let go of traumatic memories.

Carhart-Harris himself is interested in how psychedelics affect the brain and what environmental conditions make them most effective as medicines. He is now conducting

ILLUSTRATIONS: MARCOS CHIN

brain-imaging studies of healthy volunteers to understand what makes a trip good or bad, a dichotomy inherent to psychedelics. (British psychiatrist Humphry Osmond, MD, coined the term “psychedelic” in a 1956 letter to Aldous Huxley, writing, “To fathom Hell or soar angelic, just take a pinch of psychedelic.”) He also plans to design a new dosing room with high-definition visuals and sounds and curated scents to create more immersive therapeutic settings. “Some people say, ‘I went to a spa in Costa Rica, did three nights of ayahuasca, sat in a warm tub of water, and drank fresh mango juice,’” says Mitchell, who is collaborating with him on the project. “But what about people that wouldn’t be able to jump on a plane?”

The Road Ahead

Some researchers worry that the hype around the medical use of psychedelics will cause people to misuse them. Early studies suggest that the drugs can work as therapies, but only for certain conditions and only when taken under professional supervision. “People think it doesn’t look like the therapist is doing that much on whatever YouTube video they watched,” Mitchell says. “They’re pretty certain that their roommate could do that instead, which may work – until it doesn’t.”

Psychedelic trips can be especially distressing for those confronting deep-seated mental health issues. “The people who tend to publicly talk about the rainbows they saw are the people who had a positive experience,” Bradley says. “More than one person in our study has said that these sessions were some of the hardest days of their life. And that’s someone lying in a comfortable room with therapists around them and a doctor outside ready to respond to emergencies.”

For this reason, studies like Bradley’s are incredibly labor intensive. UCSF staff members perform medical and psychiatric screenings on all study participants and provide psychological, emotional, and health support during and following trips. A single trip can last for six to eight hours, so the dosing process takes all day.

The work is also expensive. The federal government rarely awards grants for psychedelics research, and many private foundations are wary of supporting drugs that still bear some stigma, so investigators rely primarily on individual philanthropists. This puts pressure on researchers and even participants. Some patients feel guilty if they don’t have positive experiences, Woolley says. “They don’t want to let the science down.”

“Expectations have been set very high,” Carhart-Harris agrees. “There are clear ways in which psychedelics could be superior to current treatments in psychiatry, but we want to be accurate.” And gathering accurate, evidence-based data takes time.

Laws around the use of psychedelics, meanwhile, are changing fast. Oregon, for example, recently legalized psilocybin services for adults. Indigenous populations and other communities around the world have long used psychedelics safely, Anderson points out, but there’s no model for their safe use in mainstream Western culture. Along with Mitchell and others, he is investigating the long-term outcomes of people who use psychedelics in recreational and other nonmedical settings, which he hopes will help inform regulatory policies.

Yet despite the challenges, those who have benefited from experimental psychedelic therapy see its promise for helping others. For many study participants, the experience has had “long-, long-, long-lasting effects,” as Solis puts it. A couple of years ago, for instance, when he heard that his eldest brother had had a stroke, he remembered his psilocybin trip at UCSF. This was the brother who had appeared to him most clearly. For the next year and a half, Solis helped care for him. “When he realized that he was going to pass,” Solis recalls, “he grabbed my hand, looked me straight in the eye, and said, ‘Please help me.’ And I was there.” He credits the psychedelic therapy for allowing him to be so present.

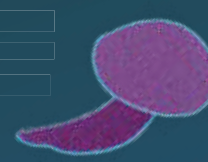
“You see the true nature of things,” he concludes. “You see the true color of things. You see the death of things, but you also see their birth.”

How do psychedelics work?

One of the leading theories posits that psychedelics temporarily change our brains so that we can let go of prior associations and acquire new beliefs. UCSF’s Robin Carhart-Harris developed this theory, called Relaxed Beliefs Under Psychedelics (known as REBUS), while he was at Imperial College London. By taking fMRI scans of people’s brains while they were on psilocybin, he found that subjects’ brain activity during their trips was dysregulated, or impaired, compared to when they were sober.

The reason may have to do with biochemistry. Classic psychedelics bind to 5-HT_{2A} serotonin receptors, cellular proteins that play a role in cognitive flexibility – basically, our willingness to change our minds or think differently. These receptors cluster in an area of the brain called the default mode network (DMN), which is responsible for high-level consciousness, including sense of self and autobiographical memory (think of it as your ego center). A hyperactive DMN may give rise to excessive rumination and negative self-thinking – features of depression, addiction, anxiety, obsessive-compulsive disorder, and many other mental health conditions.

So when DMN activity is dysregulated by psychedelics, Carhart-Harris speculates, those depressive thought patterns weaken, freeing the brain to make new, healthier connections. He believes this neural relaxation may also allow the rational parts of the brain to communicate more fluidly with its instinctual parts, such as its limbic system. Such changes may explain why psychedelics can foster a childlike sense of joy or enable people to revise past convictions and even politics.





The Radical Compassion of Awake Brain Surgery

On the operating table and inside the lab of a rising star in cancer neurosurgery.

By Ariel Bleicher

Portraits by Gabriela Hasbun



On a clear day in October, Shawn Hervey-Jumper, MD, rises before dawn at his home in the Oakland hills, a one-time horse ranch that he shares with his wife, two daughters, and a menagerie of animals, including a dog, three goats, and two kittens named Pepper and Cobbler, after his grandmother's peach cobbler. He packs a raspberry yogurt and a mug of black tea. Then he heads to the Helen Diller Medical Center at UC San Francisco, where he will attempt to excise a deadly tumor from a conscious human brain.

Hervey-Jumper specializes in awake brain surgery, in which patients are alert and engaged during parts of the procedure in order to prevent severe brain damage. His patient this morning, Gina, is 31 years old. It's not her first time under Hervey-Jumper's knife. Six years ago, after she had a seizure following a car accident, doctors discovered a mass the size of a plum in the top left lobe of her brain, near the areas that regulate movement and speech. The tumor had been spreading slowly, but there was no cure. Without surgery, she was told, she might still have several years left to live; an operation could double that time, or maybe more. Hervey-Jumper had removed the original mass, but like crabgrass, the cancer sprouted back around the hole.

Now, in the operating room, Gina (whose name has been changed to protect her privacy) rests inside a cave of blue surgical drapes. She lies on her right side, facing the cave's opening, her skull secured with a clamp. An anesthesiologist perches before her, monitoring her vital signs. At her back, on the other side of the drapes, technicians and research assistants lay out instruments and tend to various machines. Standing at the crown of Gina's head, Hervey-Jumper peers down through a window in the drapes onto a shaved patch on her scalp. With a gloved hand, he touches a scalpel to her pale skin.

For the moment, Gina sleeps. Over the years, Hervey-Jumper has gotten to know her well. He knows that she is close to her mother and sister and has been helping to raise a young niece. Her vibrant personality reminds him of his grandfather, who was full of love and life—someone he liked to “kick around with.”

Hervey-Jumper lived with his grandparents, Perry and Charlotte Hervey, for the first years of his life. Perry, a custodial worker who planted a peach tree in their yard, was diagnosed with pancreatic

cancer when Hervey-Jumper was 4. What scared him more than his grandfather's impending death was the way the disease diminished him. “He lost a bit of himself,” Hervey-Jumper says. He hopes to spare Gina from such an experience for as long as he can. If this surgery goes well, he believes she will see her niece grow up.

He slices through her numbed scalp smoothly, swiftly, assuredly. The blade cuts an arc that follows the earlier incision. Then he peels back the flesh to expose dull, beige bone. “We're going to drill,” he tells the room.

Meanwhile, as her sedation is turned off, Gina begins to gradually wake up.

Extraordinary Feats

At age 43, Hervey-Jumper is the latest in a long line of UCSF neurosurgeons known for removing tumors once deemed inoperable. A soft-spoken man with broad shoulders and a round, youthful face, he grew up in rural Massachusetts, in a town surrounded by cranberry bogs. After he was born, his mother enrolled in nursing school, and he often tagged along with her to clinics and seminars, which kindled his interest in medicine.

“Early on, I thought I wanted to be a surgeon,” he says. “I don't really know why. I liked working with my hands, taking stuff apart, just tinkering with things.” He went to college at Oakwood University, a historically Black university in Alabama, and then earned his medical degree at Ohio State. In 2013, after a neurosurgery residency at the University of Michigan, he was offered a fellowship to train in complex brain tumors at UCSF, which had a reputation for producing superstars in the field.

The most famous was Charles Wilson, MD, who founded what's now the UCSF Brain Tumor Center. Wilson came to UCSF in 1968 and chaired the Department of Neurological Surgery for 29 years. Also a skilled pianist and avid marathoner, he was a virtuoso of the transphenoidal resection, an operation to excise pituitary tumors through the nose. At the peak of his career, he performed as many as eight procedures a day, sometimes working in three operating rooms simultaneously; by the time he retired, in 2002, he had done more than 3,300.

“Charlie was a force to be reckoned with,” Wilson's successor, Mitchel Berger, MD, said after Wilson's death in 2018. By then, Berger—who had turned to neurosurgery after a failed bid at professional football—had become his own reckoning force. He had done his residency at UCSF and, in 1997, replaced Wilson as department chair. Like Wilson, he refused to accept that some tumors simply couldn't be taken out safely.

Berger was particularly drawn to cancers that encroach on parts of the brain responsible for language, sensation, and motor control. At the time, most surgeons believed that operating extensively in these so-called eloquent areas was too dangerous; patients could be paralyzed or their speech impaired. “In those situations, the main goal of surgery



was to get a diagnosis,” says Susan Chang, MD, a neuro-oncologist and the Lai Wan Kan Professor, who has worked at UCSF for 30 years. “You’d take a sample of the tumor – a little wedge – and analyze it to make treatment recommendations.”

But the treatments – radiation and chemotherapy – were largely ineffective. “Our patients were dying,” Berger recalls. “They died quickly after their diagnosis. I came to the conclusion that enough is enough; we weren’t getting anywhere doing the same-old, same-old.” He wanted to go after such tumors more aggressively and

thought he could do it without harming patients neurologically.

Since the late 1970s, epilepsy surgeons had been using a radical technique called brain mapping to identify and avoid eloquent areas while extracting brain tissue that was causing patients’ seizures. They would rouse a patient during surgery and, with an electric wand, briefly stimulate brain regions near the diseased tissue to see the effect. If a leg jerked or the patient garbled a word, for instance, they knew to leave the stimulated region alone. Berger convinced his former mentor, George Ojemann, MD, a brain-mapping pioneer at the University of Washington, to help him adapt the technique for tumor surgeries.

“We basically wrote the book on mapping for tumors,” says Berger, who now directs the UCSF Brain Tumor Center and is the Berthold and Belle N. Guggenheimer Professor. (He stepped down as department chair in 2020.) In study after study, Berger and his colleagues showed that the more cancerous tissue they removed, the longer patients lived – in some cases, another 10 to 20 years. Even more remarkably, as oncologists like Chang were shocked to find, patients’ cognitive abilities remained generally intact.

“I remember looking at the scans postoperatively and thinking, ‘Oh, my gosh, this person isn’t going to be able to talk because there’s a giant space where you would have expected

the language function to be,’” Chang recalls. “Then I’d go into their room, and they’d say, ‘Hello, Dr. Chang,’ and I’d think, ‘How is this possible?’ It really was a paradigm shift in how we take care of these patients.”

Mapping the Mind

Back in the operating room, Gina stirs. “You’re going to hear a loud noise,” Hervey-Jumper warns her. “Your teeth may chatter.” He wants to be sure she’s not startled as she comes back to consciousness. With the help of a resident, Winward Choy, MD, he resumes drilling. The sharp, tangy smell of bone dust – like Cool Ranch Doritos, medical students say – fills the air. The surgeons carve out a square of skull slightly smaller than a shirt pocket and are breaching the dura, the brain’s cloth-like covering, when Gina begins to shake.

“Am I moving too much?” she asks, her voice gravelly with sleep.

“It’s really normal,” Hervey-Jumper assures her – a common effect of coming off anesthesia. “Give it a few minutes, and it will go away. Do you want to listen to some music?” he offers, thinking it may help calm her.

“Not the sad stuff,” she says.

Classic rock plays over the loudspeakers: *Dancin’ in the moonlight. Everybody’s feelin’ warm and bright...*

The surgeons carry on. Hervey-Jumper delicately lifts the rubbery dura, revealing a black hollow where the original tumor had been. Soft, furrowed tissue peeks around the crater’s rim. Glistening white and crisscrossed with fine red veins, it pulsates gently: Gina’s mind.

Soft, furrowed matter peeks around the crater’s rim. Glistening white and crisscrossed with fine red veins, it pulsates gently: Gina’s mind.

“You’re doing so good,” the circulating nurse, Jennifer Mitchell, RN, tells her. She holds Gina’s hand. “Deep breaths,” Mitchell says. “In through your nose and out through your mouth.” She asks Gina what she would be doing today if she weren’t in the hospital. Visiting her niece, Gina says. It’s nearly the little girl’s birthday, she adds. She bought her a doctor play set.

Then the music stops. “The hard part’s over,” Hervey-Jumper informs her. “You just have to do some naming.”

He is ready to begin mapping her brain. First, he wants to test various tasks without stimulation, to get a baseline. He will start with language. His research assistant, Jasleen Kaur, shows Gina pictures on a laptop.

“Tell me what you see,” Kaur says. A lion, a horse, a goat, the moon...

They proceed to an auditory task. “A food that is eaten by a monkey,” the laptop recites. “Banana,” Gina answers. “A thing that strikes before thunder...”

They had planned to test her sense of touch next. But Hervey-Jumper can see that the tumor doesn’t reach as far into the sensory areas as brain scans had suggested. “It looks very separate from sensory,” he tells her. “It’s really growing back and toward your language.” Another ball of tumor worms deep into the motor areas from the bottom of the cavity, but he will tackle that later. “Let’s move on,” he says.

On the brain’s naked surface, he neatly arranges an array of sterile paper tabs. Numbered 20 through 29, they look like discards from a

“The hard part’s over,” Hervey-Jumper informs her. “You just have to do some naming.” He is ready to begin mapping her brain.



Hervey-Jumper founded the Glial Tumor Neuroscience Program in 2022 to study the relationship between brain tumors and neurons, with the aim of improving patient outcomes. “For the longest time, people have thought about the brain and cancer as two separate things,” he says. “In fact, there are very important interactions that may give us clues about how to restore or preserve cognitive functions.”

hole puncher. As he charts his course into the tumor, the numbers will be his landmarks.

“Gina, if you had trouble word-finding in Spanish, how much would that impact your life?” he asks. “Moderate or a lot?”

“Moderate,” she says.

“And if you had trouble word-finding in English?”

“A lot.”

“Okay, perfect. We’ll do English, then Spanish, in that order.”

People who learn multiple languages young – before around age 10 – use different parts of their brain for each one. Because Gina grew up speaking both English and Spanish, Hervey-Jumper will need to map each language area separately. He reaches for an electric stimulator called an Ojemann probe (after Berger’s mentor). Shaped like a large pen, it delivers a current gentler than a cell phone vibration. He touches the probe to Gina’s brain beside tab number 20. (There are no nerve endings in the brain itself. “You could stick your finger into your brain, and you wouldn’t feel a thing,” Hervey-Jumper says.)

“Twenty,” he announces to his team, and a picture flashes on the screen in front of her.

“Trumpet,” she says.

PHOTO: GABRIELA HASBUN



“Twenty-one.”

“Seal.”

“Twenty-two.”

“Baby carriage.”

“Twenty-three.”

The stimulation can disrupt a patient’s speech in a variety of ways. Sometimes they say the wrong word (“dog” when they’re shown a cat, for example). Sometimes they mix up the word (“kit” instead of “cat”) or draw it out (“caaaaat”). Sometimes they hesitate. Sometimes they perseverate, repeating the same answer again and again. Sometimes they don’t answer at all.

Such mistakes indicate which numbered brain regions Hervey-Jumper will need to bypass. But Gina performs flawlessly – except for one forgotten Spanish word (“trompeta”), a language in which she’s not fully fluent. His path into the tumor is safe.

“Okay, Gina,” Hervey-Jumper says, “we’re going to start to turn your sedation back on – but very slowly, because I want to talk to you while we do the next step.”

“What’s the next step?” she asks.

“The next step is we take this monster out of your head.”

An Insidious Disease

In addition to running a high-stakes surgical practice, Hervey-Jumper has distinguished himself as a pioneering neuroscientist. After completing his fellowship at UCSF in 2014, he joined the faculty at the University of Michigan, where he started a research lab to study the brains of cancer patients with the aim of improving their outcomes. Brain mapping had made life-prolonging surgeries possible by preventing catastrophic neurological injury, but most patients still lost some function, often in ways that were difficult to predict.

Once, for instance, Hervey-Jumper operated on a middle-aged man, an ophthalmologist and fly-fisher, who had developed a tumor above his left ear, in the brain area that controls the right hand. “I said, ‘Listen, we can remove this thing, but you probably won’t have full dexterity in your hand,’” Hervey-Jumper recalls telling the patient. “‘It’ll move, but it won’t do detailed work.’” Three months after the surgery, the patient emailed him a video. “He was tying a fly!” Hervey-Jumper relates. “I was shocked, because right around this time, I had another patient who had a tumor in the exact same location. It was nearly the same operation, same everything. One patient is fly-fishing and the other can’t even write.”

He wanted to understand why. “I thought there must be some underlying differences that cause some patients to recover to a fuller extent than others,” he says. He first tried looking for genetic factors, but after two years, he hit a dead end and decided to change tack.

By then, he had moved to UCSF, where he is an associate professor. Berger, who had trained Hervey-Jumper during his fellowship, had fought hard to recruit him. “I sensed that he was an extraordinary individual,” Berger says, “not just in terms of his technical skills but also in his ability to think outside the box.” Hervey-Jumper has cultivated this quality by surrounding himself with other out-of-the-box thinkers. Berger is one of them. Another is Michelle Monje, MD, PhD, a pediatric neuro-oncologist and neuroscientist at Stanford, whom he sought out as a mentor and collaborator.

Starting in the mid 2010s, Monje’s lab and others discovered that brain tumors called gliomas form a curious relationship with neurons in mice. Gliomas, which make up 80% of human brain cancers, arise from cells that are developing into glia, brain cells that manage neural connections. These lethal tumors don’t destroy neurons like bombs but instead invade them like weeds. Even more surprisingly, as the mouse studies revealed, glioma cells can cause neurons to fire more readily; in turn, this neural activity makes fast-growing tumors grow even faster.

Hervey-Jumper was intrigued. If neither genes nor gross anatomy could predict how a brain cancer patient would fare after surgery, he wondered, maybe something about their brain’s circuitry could. On Monje’s advice, he set about trying to replicate the mouse observations in his human patients. Using electrodes placed on the brain during surgery, he recorded neurons firing in the brains of glioma patients while they were awake and resting. Sure enough, cancerous brain regions



He vacuums deeper and deeper, closer and closer to the corticospinal tract. Then he stops. He is 5 millimeters away.

were more active than healthy regions. But what did that mean for cognitive tasks like word-finding or fine motor movement?

“That’s where Eddie came in,” Hervey-Jumper says. Edward Chang, MD, a UCSF brain surgeon who did his residency under Berger, is now the Joan and Sanford Weill Chair of Neurological Surgery. Also a neuroscientist and the Jeanne Robertson Distinguished Professor of Psychiatry, Chang (who is not related to Susan Chang) has become the world’s leading expert in understanding how the brain generates speech. Researchers in his lab are so adept at capturing and deciphering patterns of activity in the brain’s language areas that they can decode entire words from these neural signals. They piggyback these experiments onto awake surgeries for epilepsy or cancer, discarding any signals from diseased brain tissue.

But those are precisely the signals that Hervey-Jumper was interested in. “Rather than throw out the tumor data, assuming it’s garbage,” he proposed, “let’s look at it specifically.”

With Eddie Chang’s guidance, Hervey-Jumper’s team began examining neural signals from patients like Gina who had gliomas in a speech area of their brain. What they found was astonishing. When a patient started to say a word, for instance, the tumorous area lit up in sync with the tissues around it, implying that neurons subsumed by cancer still behave somewhat like normal neurons. “That freaked me out,” Hervey-Jumper says, “because if you talk to these patients, their speech isn’t normal; they have a lot of impairments.”

Analyzing the speech signals more closely, however, the team saw that those from tumor-infiltrated neurons lacked intelligible information, like a staticky radio channel. Even Eddie Chang’s well-honed decoders couldn’t tell from the staticky signals whether patients were saying simple, monosyllabic words like “cat” or more complex, polysyllabic words like “aardvark.” Their tumors, it appeared, had rewired their brains like a careless electrician.

“These are incredibly exciting, mind-boggling discoveries,” Monje says. “They show that gliomas change not only the activity of neurons but also their connectivity; these tumors can remodel neurocircuitry in a way that is advantageous to the tumor but not necessarily to cognition.” She adds, “It’s very insidious.”

Since publishing his team’s initial findings in 2021 in *Proceedings of the National Academy of Sciences*, Hervey-Jumper launched the Glial Tumor Neuroscience Program to further explore the mechanisms involved. “For the longest time, people have thought about the brain and cancer as two separate things,” he says. “In fact, there are very important interactions that may give us clues about how to restore or preserve cognitive functions.”

As much as the prospect of death, he has learned, it’s brain cancer’s ability to hijack the mind that makes the diagnosis so devastating. “He tells me it’s one of the ugliest diseases he’s ever seen,” says Heather Hervey-Jumper, MD, a UCSF anesthesiologist and his wife of 21 years. “I think that’s why he likes the lab. You go into the operating room to face the beast, but the lab is where you find hope.”

PHOTOS: MARCOS SANCHEZ, UC REGENTS

Removing the Monster

As the sedative slips into Gina's vein, Hervey-Jumper starts in on the piece of tumor just below her brain's surface, near the language areas. "I'm going to ask you silly questions so I can hear the fluency of your speech," he tells her. He excavates as they talk, listening for trouble. He does not cut out the cancer but vacuums it up with a suction tool. Steadily, he sucks away the silky white flesh, taking care to avoid two large blood vessels snaking over it.

"Oooh, I felt that," Gina says.

"I think the headache experience just spiked," someone remarks. Local anesthesia can block sharp pain, but patients still feel a dull, mounting ache. Hervey-Jumper will soon need to let Gina sleep again. "People can't just persist like that forever," he says. "You only have a finite window."

After he's removed the first mass, he turns his attention to the dark underbelly of the cavity, where the rest of Gina's tumor awaits. Here, the cancer sprawls around the corticospinal tract, a thick fan of neural fibers that connects the motor areas on the left side of the brain to the muscles on the right side of the body. Hervey-Jumper must navigate

this precarious landscape a millimeter at a time, mapping the terrain as he tunnels through it.

With a stimulator – this time a device called a monopolar probe – he sends a beam of electricity into the wall of tumor before him. The strength of the current determines the distance it travels: 1 milliamp, for example, will travel 1 millimeter. Two neurophysiologists – John "J.P." Clark, PhD, and Yanling Wang, MD – dial up the current until it strikes a bundle of motor fibers, causing the corresponding muscle to contract. Such movements are typically too small to see – sometimes a finger twitches or a lip curls – but they can be detected through electrodes stuck like postage stamps all over the patient's body. "Threshold is 10 on lower leg," Wang calls out, and Hervey-Jumper knows he is 10 millimeters – about the width of a paper clip – from the neurons that control Gina's leg.

Berger once told him that doing awake surgery is like flying a plane at night: You have to trust your brain-mapping data the way a pilot trusts their aircraft's radar system. He sucks up a speck of tumor and stimulates again. "Now 8.5," Wang says.

They continue like this as Hervey-Jumper vacuums deeper and deeper, closer and closer to the corticospinal tract. Then he stops. He is 5 millimeters away.

"Gina, can you wiggle your toes for me?" he says. "Can you point your toes toward your nose? Good," he concludes. "I don't want to go too much further or you're going to have a drop foot. If you need to run, you'll still be able to run." But, he continues, "let's see what else we can get."

He picks his way cautiously along the tumor's margins, shaving off another millimeter here, another there.

"Okay, we're done," he says at last. "We shouldn't go any further."

Gina drifts out of consciousness. In the following days, as her brain swells from the surgery, she will have some trouble walking and will struggle to find the right words, but these impairments will be only temporary. Hervey-Jumper replaces her dura, bone, and scalp and leaves Choy, the resident, to sew the last few stitches. His next patient is waiting for him.



Hervey-Jumper applies a mild electric current to a patient's brain near each numbered tab to see how it affects their speech. If they garble a word, for instance, he knows to leave the stimulated brain area alone.

**“Okay, we’re done,”
he says at last.
“We shouldn’t go
any further.”**

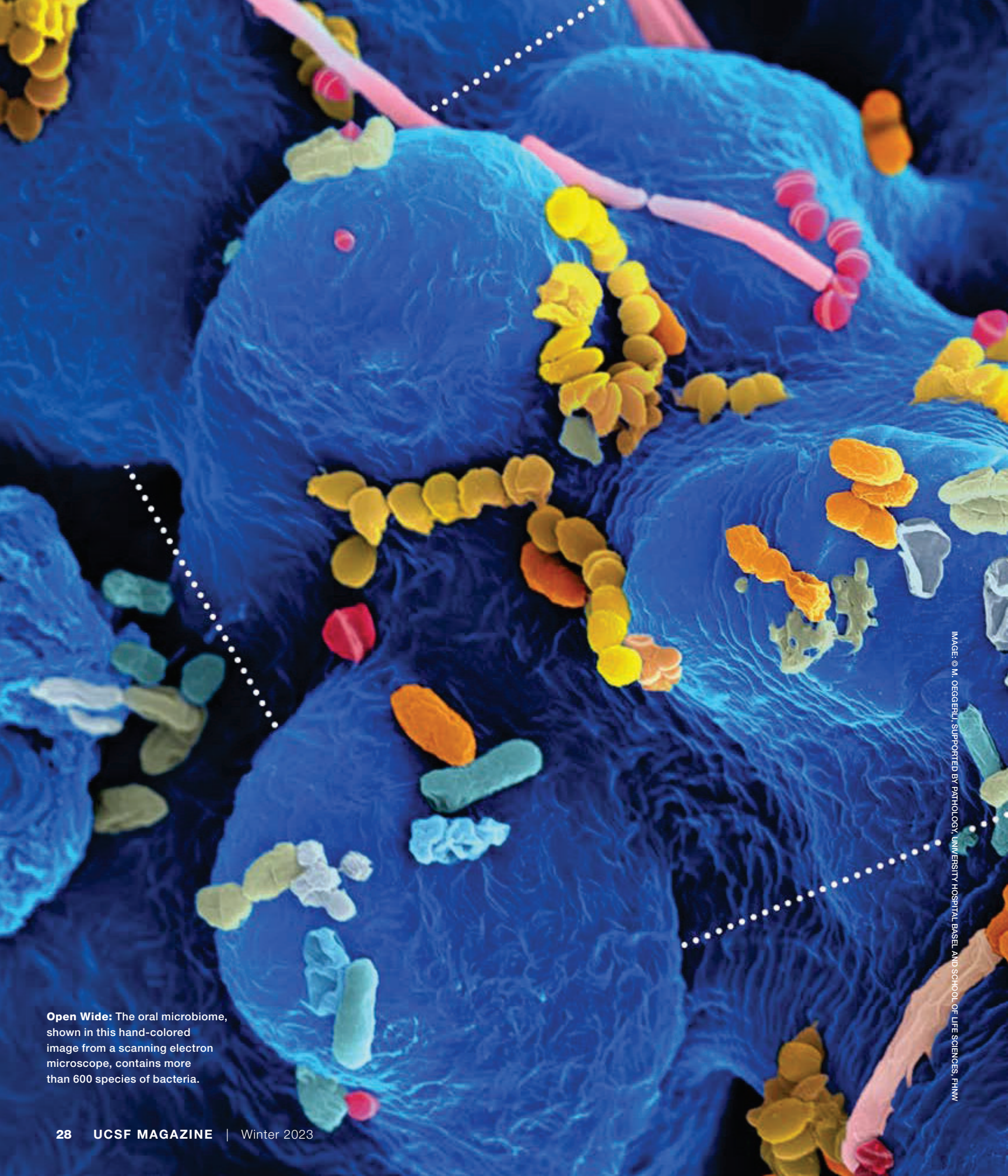


IMAGE: © M. OEGGERLI, SUPPORTED BY PATHOLOGY, UNIVERSITY HOSPITAL BASEL AND SCHOOL OF LIFE SCIENCES, FHNW

Open Wide: The oral microbiome, shown in this hand-colored image from a scanning electron microscope, contains more than 600 species of bacteria.



BIG

LITTLE

LIVES

Trillions of invisible organisms make up the human microbiome. Now, medical scientists want to put these bugs to work.

By Elizabeth Preston
Images by Martin Oeggerli

WE ARE NOT ALONE.

But you probably knew that already.

Our own bodies teem with life. Our intestines are packed with thriving invisible ecosystems. Our skin crawls with tiny critters. Our mouths are a jungle. Microbes – mostly bacteria, but also other minuscule beings such as viruses and fungi – live in our ears, noses, genitals, and lungs. They even travel in breast milk.

The field of modern microbiome science is only about 15 years old, but what we've learned in that time is absolutely staggering, says Susan Lynch, PhD, who directs UCSF's Benioff Center for Microbiome Medicine. Scientists have surveyed microbial life on virtually every surface of the human body and in nearly all its nooks and crannies. They estimate that as many 1,000 species of bacteria alone may inhabit just one person. These tiny tenants are about as numerous as our human cells, and their genes may outnumber our own a hundredfold or more.

But these bugs aren't just along for the ride. Starting at birth or even earlier, they help train our immune systems to distinguish friend from foe. They help us break down food. They even manufacture molecules that neurons in our brains use to communicate. Given the remarkable symbiosis between our bodies and their microbial communities, scientists often refer to the human-microbiome team as a "superorganism."

Teasing apart the connections between our microbiomes and our health can be tricky, however. It's not always clear, for example, whether changes in a sick person's microbiome have caused their disease or whether the disease – or something else – has changed their microbiome. Further complicating matters is the fact that everyone's microbiome is different. The makeup of your microbial zoo depends on factors particular to you, such as your diet, age, and where you live. Consequently, what makes a microbiome "healthy" or "unhealthy" most likely varies from person to person.

Still, experts are starting to piece together the puzzle. At the Benioff Center for Microbiome Medicine, more than 130 scientists are working together – like a superorganism themselves – to unlock our microbes' secrets and turn those insights into new therapies. The following are eight areas of research that offer tantalizing evidence of how our microbiomes influence our health, and how we might one day manipulate them to prevent and treat disease.

"WE'RE TRYING TO BUILD HEALTHY MICROBIOMES FROM THE VERY EARLIEST STAGES OF POSTNATAL LIFE."

SUSAN LYNCH, PHD

DEPRESSION BACTERIAL BLUES

If you've ever experienced depression, you know it's not just "all in your head." It isn't even all in your brain.

"Depression is truly a whole-body disease," says Ryan Rampersaud, MD, PhD, an assistant professor of psychiatry at UCSF's Weill Institute for Neurosciences. This common mood disorder has been linked to a range of biological and environmental factors – including, he points out, your gut bugs.

In a 2016 study, scientists found that the digestive tracts of people with depression harbored microbial ecosystems that were less diverse than those of healthy controls (think city park versus rainforest). Then the scientists transplanted stool from the depressed humans into the stomachs of rats. Subsequently, the rats exhibited "depression-like" behaviors, such as avoiding open spaces (suggesting anxiety) or losing interest in drinking sugar water (loss of pleasure) – evidence that the makeup of our microbiomes can influence our moods.

But how do our microbes talk to our brains? Studies show that gut microbes can trigger the intestines to release molecules called neurotransmitters that the brain uses for signaling, including serotonin and gamma-aminobutyric acid. Many gut microbes even make neurotransmitters themselves. Some of these molecules then seep into the bloodstream and travel to the brain, where they might affect how we think or feel. A 2019 study found that some bacterial species were less abundant in people with depression. And people whose microbiomes were more capable of making a molecule related to the neurotransmitter dopamine reported a higher quality of life.

In his own lab, Rampersaud is studying the microbiomes of people with depression before and after an eight-week course of antidepressants. He wants to identify any changes in their microbiomes as their depression lifts. For example, he may find that a certain bacteria-made molecule is lacking in depressed patients but increases as their mood improves. If that's the case, he imagines, doctors could one day supplement depression treatments with probiotic pills containing bacteria that make the depleted molecule.

"What I hope is that we can help alleviate suffering," Rampersaud says.



WHAT MAKES A “HEALTHY” MICROBIOME?

The short answer is that no one really knows – at least not yet.

“We’ve learned a lot about what can go wrong with the microbiome,” says UCSF’s Peter Turnbaugh, PhD. But despite the boom in microbiome research over the past decade, today’s scientists can’t tell you precisely what to eat or buy to nurture your microbes in ways that promote health.

“I’d be skeptical of anyone who claims they know the ‘right’ diet for your microbiome,” Turnbaugh says. That’s because our microbial communities are just as unique and unpredictable as we are. “The microbiomes of healthy people vary tremendously, both between individuals and over time,” he says. So no one can define exactly what a healthy microbiome looks like for a particular person at a particular moment. And no one can say precisely how to feed your microbiome to make it act a certain way.

Even so, it appears that there may be benefits to eating dietary fiber, which is found in vegetables, fruits, whole grains, and other plant-based foods. We can’t digest fiber on our own; our gut bacteria chew it up for us. There is some evidence that the molecules these bacteria

produce when they break down fiber help lower inflammation and keep blood sugar under control. But not all fiber is the same, Turnbaugh warns, and different types – as well as other components in fiber-rich foods – may interact with our microbes in ways that are less understood.

What about probiotics? A host of pills, yogurts, and lotions promise to boost our health through the power of microbes. But like other supplements, these products aren’t regulated by the Food and Drug Administration. That means there’s no guarantee that a product actually contains the bacteria it claims to, or even if it does, that those bacteria will help you. (If you want to learn what’s in a particular product and the science behind it, Turnbaugh recommends the website usprobioticguide.com.)

With everything scientists are discovering about the role our microbiomes play in our health, we all want to know how to keep these bugs functioning at their best. But microbiome medicine likely won’t lead to simple, one-size-fits-all solutions. “The reality is a lot more complicated,” Turnbaugh says. “There’s always more to learn.”

Navel Gaze: Scientists have found thriving microbial communities on virtually every surface of the human body and in nearly all its nooks and crannies, including the belly button (shown here).

GUM DISEASE

DOWN IN THE MOUTH

You may have a separate insurance plan for your teeth, but the health of your mouth is tightly tied to the health of the rest of your body. “The two are intertwined in so many ways,” says Yvonne Hernandez-Kapila, DDS '90, PhD '97, the associate dean for research at UCLA School of Dentistry and a UCSF adjunct professor of orofacial sciences.

Heart disease, for example, is unusually common in people with gum disease. So are certain cancers. Scientists are still unpacking the mechanisms behind these connections, but Hernandez-Kapila believes mouth microbes are at least partly to blame.

Consider gingivitis, she says. This inflammatory gum disease, and its worse form, periodontitis, are linked to worrisome changes in the oral microbiome: Certain unfriendly bacteria proliferate, suppressing friendly bacteria. Studies suggest that this shift elicits chronic inflammation, which can cause bone loss. Heart disease and other internal ailments might arise when bad bacteria that multiply in the mouth – along with the molecules they make – leak into the bloodstream and travel around the body, stirring up more trouble wherever they land.

In experiments in mice, Hernandez-Kapila showed that bacteria associated with gum disease can also encourage the growth of cancers in the head and mouth. These discoveries have led her to a potential new cancer therapy. By treating the mice with nisin, a molecule made by certain bacteria and able to kill other bacteria, she found that she could shrink the animals' tumors.

“We can specifically target microbiomes to change the course of the disease,” Hernandez-Kapila says. In collaboration with her UCSF colleagues, she is now launching a clinical trial of nisin in patients with oral cancer. She wants to see how the molecule alters their mouth microbiomes and whether the tumor-shrinking powers observed in mice hold true for humans, too.

ECZEMA

SURFACE TENSION

No matter how thoroughly you scrub yourself in the shower, your skin still bustles with microbial life. And that's a feature, not – ahem – a bug.

The skin microbiome has many benefits, including keeping harmful bugs out. “It's doing a lot for us, even if we can't see it,” says Tiffany Scharschmidt, MD '08, a UCSF associate professor of dermatology.

Scharschmidt studies the relationship between skin microbes and inflammatory skin diseases like eczema. Scientists have long known that the immune system participates in these diseases, she says. “What we're trying to understand is how the microbiome plays a role.”

Early in our lives, Scharschmidt notes, our immune systems learn to recognize our skin's microbial inhabitants as what she calls “part of the broader self” and to coexist with them peacefully. But what happens if this rapport turns sour? Say, for instance, the makeup of these microbes shifts later in life. Could that change nudge our immune systems toward misbehavior? Could inflammation and disease follow?

The microbial ecosystem in the gut might also contribute to immune dysregulation in the skin. In a 2022 paper, Scharschmidt's team showed that chronic inflammation in the intestines of mice caused inflammatory molecules to migrate to the skin, prompting immune cells there to attack friendly bacteria. This immune system mischief also led to skin inflammation.

Scharschmidt hopes to learn how our immune systems communicate with our skin bacteria in times of good health as well as bad, which includes deciphering the precise immune cells and processes involved. “The overarching question,” she says, “is ‘Can we decode this language?’”

MULTIPLE SCLEROSIS

BUILDING UP THE NERVES

Recently, Sergio Baranzini, PhD, the Heidrich Family and Friends Professor of Neurology at UCSF's Weill Institute for Neurosciences, led a study looking at the microbiomes of more than 500 people with one thing in common: multiple sclerosis, or MS.

In MS, a person's immune system attacks the protective sheath around nerve cells in their brain and spinal cord. This can cause a range of symptoms, including vision problems, pain, fatigue, and loss of muscle control.

Because our gut microbes interact closely with our immune systems, Baranzini wonders whether variations in the makeup of our microbiomes could increase our risk of MS and other autoimmune conditions. It's possible that the molecules those bacteria make could be more important than the actual species of bacteria. “Sometimes,” he says, “it doesn't really matter who's there, as long as a particular function is being provided.”

Baranzini's lab and others have begun gathering compelling evidence that gut microbes play a part in MS alongside other known risk factors, including genetics, smoking, and infection with the Epstein-Barr virus. The new study, published in 2022 by a global consortium of labs that Baranzini leads, was the largest of its kind to date. The researchers found several types of bacteria, along with molecules made by bacteria, that were either more or less prevalent in MS patients than in healthy subjects living in the same house.

These differences might encourage inflammation, the authors wrote, and make the effects of MS worse. They hope the findings can lead to “designer probiotics” that improve the lives of MS patients.



ALLERGIES & ASTHMA

BUGS TO HELP YOU BREATHE

We acquire our first microbes from our mothers, during birth or even in utero. Over our first years of life, our microbiomes rapidly diversify, and these germs provide our developing selves with a “library of microbes,” says Susan Lynch, which trains our immune systems to tolerate their presence.

This early microbial education, she adds, may explain why babies delivered vaginally are less likely than those born by cesarean section to acquire allergies or asthma in childhood. Without that early conditioning, the immune system can mistake a harmless substance, such as pollen or pet dander, as being dangerous. (Allergies and asthma are also less common among children who grow up on farms.)

Such associations suggest that the microbiomes we cultivate as infants affect our health later in life. But how? Lynch’s own research has begun to yield some answers. In a 2016 study, she showed that patterns in the composition of the gut microbiomes of 1-month-old babies could predict which kids were at much higher risk of acquiring allergies by age 2 and asthma by age 4. The gut microbiomes of the high-risk infants were missing a wide range of anti-inflammatory molecules, she found.

Then, in a subsequent paper, Lynch identified a molecule made by the high-risk infants’ gut bacteria that seems to be responsible for the later emergence of allergies. Her team showed that the molecule travels through the blood to the airway, where it impairs immune cell activity, leading to inflammation.

In 2016, Lynch co-founded a company called Siolta Therapeutics to turn her findings into treatments. One product now in development will deliver a cocktail of live bacteria into the guts of newborns most at risk of allergies and asthma. The hope is that these bugs will start making the asthma-protective molecules that are underproduced by the babies’ native microbiomes.

“We’re trying to build healthy microbiomes from the very earliest stages of postnatal life,” Lynch says.

Newborn Bonds: Bacteria and other microbes start colonizing the human body beginning at birth, or even before. This artistically colored microscope image captures the gut microbiome of an infant one month after birth.



**“MICROBES
ARE FANTASTIC
CHEMISTS.”**

PETER TURNBAUGH, PHD



PRETERM BIRTH EARLY INFLUENCERS

About one in 10 babies in the United States is born preterm – before 37 weeks of gestation. These infants are at higher risk of disability and death. But scientists have struggled to pinpoint the causes of early birth – or ways to prevent it. That’s why Marina Sirota, PhD, a UCSF associate professor of pediatrics, is excited to have found hints to answers in the vaginal microbiome.

In a 2020 study, Sirota measured the variety of bacterial species in the vaginal microbiomes of pregnant women. In general, she says, “we think of microbial diversity as a positive.” The more diverse your gut microbiome, for instance, the more likely you are to have good blood pressure, bowel function, and other markers of health. In the vaginal microbiome, however, “diversity is actually not a good thing,” Sirota points out.

Her study showed that pregnant women with a greater diversity of vaginal microbes were more likely to deliver their babies prematurely. This correlation was strongest in microbial measurements taken during the first trimester. Sirota also found several types of bacteria that were either more or less abundant in mothers who went on to deliver preterm.

These differences, she warns, are merely associations. Sirota’s data can’t tell her whether a mother’s microbiome actually causes early birth. It’s possible that other factors in a pregnant woman’s environment, such as her diet or chemical exposures, might alter her microbiome and induce an early delivery.

Regardless, Sirota is using computer science and large microbiome data sets to identify the mothers and babies in the greatest danger. “The goal is to figure out whether we can apply machine learning and predict women who are at a higher risk of preterm birth,” she says.

DIET HEAVY QUESTIONS

You may be a vegetarian, a sushi aficionado, or someone with an unbreakable diet soda habit. Your microbes have preferences, too. In the lab of Peter Turnbaugh, PhD, a UCSF professor of microbiology and immunology, researchers are studying the relationship between diet, weight, and what our gut bacteria like to munch on. “We’re interested in how the things that we eat affect our microbes, and in turn, how the microbes affect what we eat,” he says.

For example, his team found that after just five days on a diet of meat, eggs, and cheese, people’s microbiomes looked significantly different than after five days on a plant-based diet. And the microbes that flourished on the plant-based diet produced more of a certain molecule that fights inflammation. In other research, Turnbaugh showed that raw and cooked potatoes also have differing effects on our microbial ecosystems.

Such changes to our microbiomes might influence our ability to gain or lose weight. As a graduate student, Turnbaugh led a study showing that when gut microbes from obese mice were transplanted into skinny mice, the skinny mice gained weight. More recently, in a 2021 study, his team showed that the opposite is also true: First, human volunteers consumed an extremely low-calorie, liquid diet that made them lose weight. Then the researchers placed stool from those subjects into the guts of germ-free mice. Although they were allowed to eat whatever they wanted, the mice shed weight, just as the humans had.

Turnbaugh is also exploring how our microbiomes interact with the medicines we swallow. He recently found, for instance, that certain gut bugs can break down a common cancer drug. “Microbes are fantastic chemists,” Turnbaugh says. “They are essentially stealing the drug before it reaches the cancer.”

CANCER TAMING TUMORS

Cancer, in which our bodies’ own cells change and grow out of control, might seem totally separate from the world of microbes. But in reality, “the microbiome is crucial to understanding how cancers start and progress,” says genitourinary oncologist Rohit Bose, MD, PhD, an assistant professor at UCSF’s Helen Diller Family Comprehensive Cancer Center.

Bose is investigating the connections between the microbiome and prostate tumors. Do some bacterial species cause tumors to grow faster or slower? Do microbes produce molecules that make a tumor more or less sensitive to treatment?

“There’s already experimental evidence that the microbiome changes how prostate cancers respond to therapies,” he says. Previous research has shown, for instance, that gut bacteria can make compounds similar to our own hormones, and those compounds can make prostate cancer harder to treat. Now, in collaboration with Susan Lynch’s lab, Bose’s lab is testing in mice how gut microbes, and the molecules they make, affect prostate tumor growth.

He’s also curious about bacteria that hide in patients’ urinary tracts and around the prostate itself. These microbes interact with their environment and crank out various molecules that may affect inflammation and the immune system, just as gut microbes do. “So it makes sense that they, too, would affect the initiation and the development of cancer,” Bose says.

“We’re just at the beginning,” he adds. He also believes that what he and others discover will have implications beyond the prostate. “We think it will be widely applicable to how other kinds of cancers evolve,” observes Bose.

Gut Check: A single sample of human feces (pictured on the opposite page) contains billions of microorganisms, including one of the world’s largest bacteria.



THE KIDS ARE ~ NOT ~ ALL RIGHT

Most hospitals don't adequately treat children's pain, say UCSF experts. Can their unique approach help stop the suffering?

By Alexis Martin Illustration by Brian Rea

It was February 1985 when Jill Lawson suddenly found herself in labor, three months early. Baby Jeffrey was born at Columbia Hospital for Women in Washington, D.C., at 26 weeks' gestation, weighing just 1½ pounds. He was alert and active but gravely ill.

Two weeks after his birth, Jeffrey's health took a turn for the worse: He developed a heart defect common in premature infants – patent ductus arteriosus, or PDA. Jeffrey was scheduled for open-heart surgery and transferred to the nearest children's hospital.

In those days, surgery for PDA was invasive. Holes were cut on either side of Jeffrey's tiny neck and chest to insert a catheter into his jugular vein. His little body was opened from breastbone to backbone, his flesh lifted aside, ribs pried apart, and a blood vessel near his heart tied off, and then all the tissues were stitched back together.

Baby Jeffrey felt everything – every incision, every internal repair, every stitch. The medical team had not given their fragile patient any drugs, any comfort, *anything* to protect him from the excruciating pain of open-heart surgery – just a paralyzing agent to keep him still during the procedure.

Five weeks later, Jeffrey passed away.



In the days before her child's death, Jill Lawson learned a shocking fact: Anesthetizing babies for surgery was not common practice. After Jeffrey died, Lawson called his doctor for reassurance. Surely, she thought, her child had been given *something* for the pain.

"The anesthesiologist informed me that she had not

used any anesthesia or analgesia on Jeffrey,” Lawson wrote in an account of her son’s experience. The doctor told the grieving mother it hadn’t even occurred to her to do so because it had never been demonstrated that babies can feel pain.

Jeffrey’s experience was far from unique. When Lawson took her son’s story to the *New York Times*, the newspaper found that the vast majority (77%) of newborns who underwent surgery to repair PDA between 1954 and 1983 had received only muscle relaxants and nitrous oxide, an anti-anxiety medication and very weak anesthetic. For decades, physicians routinely operated on babies with little or no anesthesia, based on the widely held belief that infants are too primitive an organism to feel pain and that potent anesthetics might kill them.

Jeffrey’s death marked a turning point. In 1987, the American Academy of Pediatrics declared it unethical to operate on newborns without anesthetics. But even today, 35 years later, disturbing echoes of Jeffrey’s experience remain: Hospitals consistently fail to fully ease the pain of their young patients.

“Study after study shows that children’s pain – whether it’s related to a procedure or an injury, chronic or acute – is vastly underrecognized and undertreated in children’s hospitals worldwide,” says Stefan Friedrichsdorf, MD, UCSF’s Stad Professor of Pediatric Pain Medicine, Palliative Care, and Integrative Medicine. “And the younger the child, the less likely they are to get the pain relief they need – whether through medications or other proven approaches to pain management.”

The implications are profound: For children, lack of pain care can lead to anxiety and depression, heightened sensitivity to pain later in life, and avoidance of health care in adulthood, including lifesaving vaccinations.



In 2010, two UCSF pediatricians – Stephen Wilson, MD, PhD, and Karen Sun, MD – began exploring what it would take to tackle this problem head-on, for every hospitalized child in pain at UCSF. They wanted to combine a range of techniques – from conventional medicines to complementary integrative therapies, such as acupuncture and massage. They consulted with Friedrichsdorf, then-director of the country’s first pediatric pain program, at Children’s Minnesota, and the world’s foremost expert on children’s pain.

“We realized that our patients needed more, that we needed to broaden our view of what pain management means and incorporate a whole spectrum of therapies,” says Sun. “We started out small, but we have been able to transform how this hospital thinks about children in pain. Our vision was to build a program that would become a destination center.”

A dozen years later, thanks to a \$3 million investment from Elisa and Marc Stad, their vision has become a reality. In 2021, UCSF launched the Stad Center for Pediatric Pain, Palliative, and Integrative Medicine, one of the most comprehensive and innovative pediatric pain programs in the country. The center brings together multiple approaches, including advanced and safe drugs, with integrative medicine, psychology, and physical therapy, to care for patients. Friedrichsdorf was recruited as the center’s inaugural medical director and chief of the Division of Pediatric Pain, Palliative, and Integrative Medicine.



Stefan Friedrichsdorf became medical director of the UCSF Stad Center for Pediatric Pain, Palliative, and Integrative Medicine when it launched in 2021. He says the establishment of the nation’s first standalone medical division devoted to pediatric pain is “groundbreaking.”



Seven years before Jeffrey Lawson was born, Friedrichsdorf was 9 years old and playing outside his home in Germany when he suddenly became sick and spiked a fever. His parents took him to the local hospital, where doctors discovered a severe infection in one of his fingers. His body was going into sepsis.

At the hospital, Friedrichsdorf was separated from his parents and brought to a surgical room. Without warning or explanation, a nurse held him down while doctors cut into both sides of his finger to drain the pus that had accumulated in it. “I was alone. I was anxious. And it was so painful. I was screaming at the top of my lungs,” he says. “And I remember to this day, that one surgeon said to the other, ‘Do you think he can feel any pain?’ and the other one said, ‘No, he can’t.’”

Friedrichsdorf developed a lifelong fear of needles and anxiety related to medical procedures, which is why his eventual decision to pursue medical school was unexpected. He experimented with a long list of other career paths before settling on life as a doctor: newspaper carrier, tour guide, factory worker, actor, journalist, children’s theater director, camp counselor, and paramedic.

It was during his time as a camp counselor that Friedrichsdorf first noticed the calming effects of mind-body techniques on children. At the end of a long day in the wilderness, his campers having been energized by hours in the elements, Friedrichsdorf used guided imagery – storytelling designed to evoke a relaxed, peaceful mental state – to help the kids calm down, snuggle into their sleeping bags, and fall asleep around the campfire. As a paramedic, he employed guided imagery again, as well as distraction and aromatherapy, to relax children in severe pain and distress.

But when Friedrichsdorf started medical school in the 1990s, he was shocked to find that children’s pain, as well as all the distress and anxiety associated with pain, was rarely prioritized in pediatric hospitals, whether through drugs, mind-body techniques, or a combination of the two.

“I SAW KIDS BEING HELD
DOWN AND SCREAMING....
I THOUGHT TO MYSELF,
'I CAN DO THIS BETTER.'”

– Stefan Friedrichsdorf, MD

“Pain control in children’s hospitals was still new,” he says. “I was working with children with cancer, but their pain was not being managed well. I saw kids being held down and screaming. Hospitals and clinics claim that they never have enough staff to provide appropriate pain control to children, but they always seem to have enough staff to hold children down. I thought to myself, ‘I can do this better.’”

Friedrichsdorf sought out training but found no coursework, no medical specialty, anywhere in Europe, devoted to pediatric pain. “Then I learned that the first fellowship for pediatric pain and palliative care was being offered at the University of Sydney, Australia, and I went for it,” he says. “It was life-changing. I worked with every single pain patient in the children’s hospital, and I realized ‘This is not rocket science. We can do this in children’s hospitals.’”



It may not be rocket science, but the science of pediatric pain is more complex than one might think.

From a biological standpoint, the basic idea is this: When a tissue injury occurs, sensory receptors in our tissues send a message to the brain, where the sensation is registered, the information is processed, and the pain is perceived. But that biological process is just one piece of the puzzle.

Friedrichsdorf likes to use a hypothetical example involving 100 children jumping on a trampoline. If all 100 sprain their ankles, why do

98 of them go on to become pain-free, but one or two of the children experience debilitating and prolonged ankle pain?

The answer is, because pain is complicated. “The severity of the injury or infection does not necessarily correspond to the personal experience of pain,” says Cristina Benki, PhD, a UCSF pediatric pain psychologist who works closely with Friedrichsdorf. “What we have to ask is ‘What are the other factors that influence that individual experience?’”

In fact, the biological aspect of the pain – the tissue damage itself – is interacting with psychological and social factors that also influence how pain is perceived. For children, feelings of pain can be deepened by anxiety and depression, as well as by social factors like how they were taught to think about pain and by family trauma like financial instability, divorce, or domestic violence.

Research shows that everything is connected when it comes to pain. “So much about pain is psychological,” says Benki. “How we experience pain is about the environment that your brain and body are raised in. How we learned to cope with stress. How our minds work – whether we tend toward more negative or positive thinking. All these factors contribute to the pain experience. But the bottom line is that the pain is very real.”

In other words, it’s possible that those children with debilitating ankle pain were going through something else in their psychology or home life – heightened stress at home, a family history of chronic pain, an anxiety disorder, or other such issues – that triggered an additional stress response in the brain that, in turn, worsened the physical sensation.

“Stress, anxiety, depression, perceived injustice, even disturbed sleep, are what we call facilitatory ascending inputs,” says Friedrichsdorf. “These are pathways in our brains – all the way from the thalamus to the prefrontal cortex – that can actually increase the perception of pain.”

The good news: “We can interrupt this process,” says Benki. “We can intervene and either change the environment or the internal experience through a combination of safe pain medications, psychotherapy, mind-body techniques like hypnosis and guided imagery, and other interventions. We can change the pain experience and help these kids get better.”



Friedrichsdorf first began using hypnosis with children in pain during his fellowship in Australia. Today, it’s an integral part of his practice at the Stad Center.

“When people think of hypnosis, they imagine I say a few magic words and snap my fingers and you then give me all your chocolate,” Friedrichsdorf says. “That’s not how it works. In my practice, hypnosis is about guiding a subject through an alternative state of awareness with the expressed, explicit purpose of reducing discomfort.”

Take Jimmy, a 17-year-old patient who has been in and out of the hospital for years with a painful gastrointestinal condition so severe that pain medications offered little relief. Friedrichsdorf met with Jimmy to learn more about his discomfort and offered hypnosis. During Jimmy’s first session, Friedrichsdorf asked him to imagine a safe and favorite place. “Are you alone?” he asked. “What do you hear? Can you smell anything? Do you feel the sun on your face?”



Jimmy, 17, practices hypnosis with Friedrichsdorf at UCSF Benioff Children's Hospital San Francisco in November. Jimmy has spent years of his life in hospital rooms for a painful gastrointestinal condition.

"SO MUCH ABOUT PAIN IS PSYCHOLOGICAL.... BUT THE BOTTOM LINE IS THAT THE PAIN IS VERY REAL."

— Cristina Benki, PhD

Having been bed-bound for weeks, Jimmy chose to go to an amusement park. He felt the wind in his hair as he wandered among the attractions. He heard children's voices rise and fall in collective excitement as a roller coaster gained speed in the distance. He breathed in the smell of popcorn and sweet treats.

With Jimmy relaxed and enjoying the park, Friedrichsdorf dug deeper. "What do you want to get rid of?" he asked. "My pain," Jimmy answered. So Friedrichsdorf asked Jimmy to imagine a trash can, put his pain into it, and destroy it. Jimmy gathered up and detonated his pain. "How do you feel?" Friedrichsdorf asked. The pain had lessened, Jimmy said, from a 10 out of 10 to a 6.

Mind-body techniques like hypnosis, guided imagery, and meditation activate the same part of the brain – known as the periaqueductal gray – that pain medications like morphine and fentanyl target. "If you have severe pain because you just burnt your leg with hot coffee and I give you some morphine, the pain goes away," says Friedrichsdorf. "If I look at what's happening in your brain at that moment, the periaqueductal gray is lighting up and decreasing the pain signals reaching your brain. If you practice hypnosis, if you do guided imagery, if you do meditation, the same part of the brain that is activated by opioids is activated by those techniques."

Friedrichsdorf acknowledges that the fear of overmedicating a small child is a legitimate concern. "But if a child has pain, it's not just about giving them medications anymore. It's about combining a lot of different modalities at the same time to provide the best possible pain control with far fewer side effects."

At UCSF, Friedrichsdorf's team of clinicians treats children in pain using a unique combination of pain medications (including analgesics

and anesthesia), integrative therapies (such as mind-body techniques like hypnosis and massage), psychotherapy (such as cognitive behavioral therapy), and rehabilitation (including physical therapy).

Their approach has yielded profound results for children, from infancy to young adulthood.



Dylan is one such patient. Dylan had been in severe abdominal pain from the time they were 2 years old. It had taken the joy out of birthday parties, family outings, play dates, and school. When a fun event approached, little Dylan grew anxious that their pain would flare and cause a scene – like the time they couldn't resist a bite of pizza at a mini-golf birthday party and ended up vomiting into a trash can while the other children looked on.

Dylan was finally diagnosed with Crohn's disease at 13 and put on opioids to control their discomfort. Whenever pain erupted, doctors either upped Dylan's dosage to alarming levels or dismissed their concerns. By the time Dylan was transferred to UCSF Benioff Children's Hospital San Francisco at 19, they were in debilitating pain, dependent on opioids, unable to walk, and deeply traumatized by a lifetime of distressing hospital experiences.

The UCSF team told Dylan the pain could be controlled without opioids, but it would take work. Dylan dove in. They committed to physical therapy despite their discomfort and came to embrace a new exercise routine. They tried acutherapy (an umbrella term that encompasses acupuncture and acupressure), massage, and art therapy, and learned how

to use drawing to distract them from the pain. And they unpacked their trauma with Benki in therapy, where they practiced techniques like deep breathing and guided meditation that they could take forward on their own.

Six months later, Dylan was off opioids, managing their pain effectively, walking with assistance, and immersed in a creative practice. “I incorporate all of it into my daily life – the techniques I did in psychotherapy, the exercises I did in physical therapy, the art, acupuncture. I don’t think I’d be able to function without that experience.”



The Stad Center’s pain specialists love sharing stories like Dylan’s: real-life evidence that their teamwork can have a life-changing impact on their young patients. But their passion is often accompanied by a sense of urgency: The demand for comprehensive pain care is enormous, and the center’s capacity to meet those needs is falling short.

In part, the challenges are structural. The health care industry has been slow to catch up to Friedrichsdorf’s vision for modern integrative pain care. Insurance companies do not reimburse for most of the Stad Center’s services, and the pool of specialists is limited due to persistent gaps in medical education focused on children’s pain. The center relies largely on private support to provide the care that gave Jimmy and Dylan relief and to conduct the training and research that advance the field. But that support is barely scratching the surface when it comes to the urgent needs of current patients.

“Like any other medicine, you want to make sure you’re giving the right dose,” says Robyn Adcock, director of integrative medicine and a pediatric acupuncturist. “But I have a limited service, so it’s always a balance: How do we share these services equitably? If you spread them too thin, they’re not effective for anyone. It’s like you don’t have enough insulin and everyone needs it. You’re only going to be able to help a few patients get better.”

Adcock and her colleagues are advocating for changes to insurance policies on the state and national levels. The team is also finding creative ways of expanding access to integrative therapies within the hospital system itself, particularly for patients who would otherwise be unable to afford such services.

Integrative medicine specialist Jenifer Matthews, MD, is based at UCSF Benioff Children’s Hospital Oakland. Matthews and her team secured a grant to offer acupuncture at the hospital’s community clinic, where 92% of patients fall below the poverty line. “It was immensely popular and helpful,” she says. But when the grant ran out, they lost their acupuncturist. “Now I offer acupuncture as much as I can ... but it’s not enough. We want to do more.”

Friedrichsdorf acknowledges that the establishment of the Stad Center as the nation’s first standalone medical division devoted to pediatric pain was groundbreaking and has the potential to transform how children in pain are cared for. But he has his work cut out for him. Reaching every patient in need with comprehensive care will take time, philanthropy, and a significant shift in national health care policy.

“In pediatric medicine, the number-one priority, of course, is still ‘Can I make this child survive?’” says Friedrichsdorf. “Comfort and pain are usually not the priority. They are certainly not a priority for insurance companies. Most of these services are not reimbursable.

“UCSF Benioff Children’s Hospitals are amazing children’s hospitals. We have thousands of clinicians and researchers who get up every morning to eradicate disease. Our team gets up every day to eradicate pain and suffering. But the only way we can do that – the only way our patients can see this team, see a psychologist, get acupuncture or massage – is through community support.

“The establishment of the Stad Center is huge, and I am so excited to be here. Things are really starting to change, but we do need community support to help our patients right now, today, and to show the world how incredibly valuable this work is.”



Massage therapist Kathleen Phelan (right) provides a gentle massage to a young patient to relieve their abdominal pain and shows their mom how to soothe the child’s pain through touch.

ALUMNI HUB

They're fixing inequities in clinical trials, bringing artificial intelligence to dental practices, speeding medicines to disaster zones, and more. Meet five impressive innovators and entrepreneurs.

Illustrations by John Jay Cabuay

GRADUATE DIVISION

Joyce Tung, PhD '05

Date with DNA Destiny

The Chinese word for cilantro translates as “fragrant vegetable.” But not if you ask Joyce Tung. She calls it “stinky vegetable.” That’s because Tung, vice president of research at the human genomics and biotech giant 23andMe, has a genetic predisposition to dislike the herb.

It’s the sort of detail you might know if you’re a geneticist — especially one who helps decide which traits are studied in 23andMe’s research program. Tung’s Bay Area-based employer is the only company authorized by the U.S. Food and Drug Administration to deliver genetic test results directly to consumers; like her, more than 13 million other people have submitted their saliva for its inspection.

While the results serve up quirky facts like cilantro aversion, fear of heights, or appeal to mosquitoes (Tung is among those likely to get larger welts from their bites), 23andMe also delivers insights that could have serious implications, such as one’s likelihood of developing type 2 diabetes, Parkinson’s disease, or late-onset Alzheimer’s.

“Empowerment is an important part of 23andMe’s ethos,” says Tung. “We want to empower consumers with information that will enable them to make better decisions. My aspiration is to help people feel confident that they can understand complicated scientific and medical information and feel like peers in health care decision-making with clinicians.”

She happened on the fledgling startup in 2006, while doing a postdoc at Stanford. After spotting a help-wanted ad pinned to a bulletin board, she replied, and in 2007, became one of the company’s first hires. Today, 23andMe is publicly traded and employs more than 700 people.

“The flyer highlighted 23andMe’s desire to use genetics to educate people about their lives,” says Tung. “I was nervous about leaving a very safe postdoc to go to a company with no website

or products. I’m not a big risk-taker, but I also thought, “This is exactly what I’m interested in doing!””

Today, she runs the company’s human genetics research program, a role that has her supervising as many as 70 scientists. She oversees data collection and guides the work of statistical and population geneticists, bioinformaticists, epidemiologists, ethicists, and program managers who work with academic and industry partners. Her team also runs an academic collaboration program that has led to most of 23andMe’s more than 200 scientific publications.

Tung recognizes the need for greater racial equity in genetic testing. She worries about the lack of diversity among research subjects both at 23andMe and in general. People of European descent are typically overrepresented in studies. As a result, application of the discoveries may inadvertently be tailored more to that group’s characteristics. “How do we diversify research participants to ensure benefits are equitably distributed? It’s not enough to have the right intentions. Are you actually doing research the right way?” asks Tung, who says 23andMe is studying ways to address the problem.

Privacy concerns over how the company uses customer data have arisen, but Tung says, “One of our core values is that behind every data point is a human being. Our principles are about transparency and choice. At the end of the day, our customers choose how their data is used.”

In 2015, 23andMe formed a therapeutics group to conduct drug discovery and development based on human genetic information, something Tung thinks deserves more awareness. For example, the company launched its first wholly owned phase I clinical trial for an investigational cancer therapy in January 2022. The company also has



a collaboration underway with GSK that includes a phase I clinical trial and over 50 preclinical programs. And 23andMe entered into an agreement with Almirall, out-licensing an antibody designed to thwart inflammatory diseases, including various dermatological conditions.

“Instead of using data from mice, flies, or rabbits, we think it’s more efficient to use noninvasive data from humans, and we think we’re going to be two or three times more likely to come up with successful drugs that way,” Tung says.

Tung believes “the sky’s the limit” for human genetic testing. “In 20, 30, or 50 years, we’ll all be sequenced at birth. The goal will be to use that information to help people live the healthiest possible lives,” she predicts.

“I feel lucky to have stumbled upon a company that I just think is super-cool,” Tung says. “It’s been quite a ride.”

■ *George Spencer*

SCHOOL OF PHARMACY

Ruth Arnold Smarinsky, PharmD '83

A Strong Force for Good

“See a need. Fill a need.” That’s the motto of Ruth Arnold Smarinsky. For the past 17 years, she has been a driving force at Direct Relief, ranked by *Forbes* as the nation’s third largest charity and the largest charitable provider of prescription drugs in the U.S. The Santa Barbara, Calif., nonprofit distributed more than \$1.6 billion worth of medicine and supplies in 97 nations in fiscal year 2022 and sent \$400 million in aid to Ukraine last year.

“When I see a problem, I’m untiring – like a bulldog sometimes, aggressive but not obnoxiously so. I don’t let obstacles stop me. I find a way to make things work,” says Smarinsky, who was named Pharmacist of the Year in 2022 by the California Pharmacists Association. “I couldn’t do any of this without teamwork,” she adds.

As Direct Relief’s longtime director of pharmacy and clinical affairs, she greatly expanded its U.S. operations while speeding its ability to respond to global crises. She oversaw the donation of millions of prescription medications, created standardized health kits for use during disasters, and forged partnerships with more than 2,000 nonprofit health centers in underserved areas.

Before she joined Direct Relief, she set up pharmacy services and clinical pharmacy systems for Venice Family Clinic, then the nation’s largest free clinic. “I like starting new, efficient programs to help people. I try to imagine each person on the other end who’s in a crisis. I want to make things easier for them,” says Smarinsky. While at Venice, she was also a volunteer UCSF faculty member and a preceptor for fourth-year pharmacy students.

A native of Antelope Valley, Calif., she was recently promoted to senior adviser at Direct Relief. In her new role, she’s tasked with envisioning future directions for the organization. She foresees bigger investments in mobile medical units and street medicine, to bring care to unsheltered people. She is allying with the European Renal Association and its Ukraine Task Force, believing that Direct Relief needs to do more after disasters to help nephrology patients and others with life-threatening diseases.

The challenges facing Direct Relief are mounting, she says. “COVID was crazy. Ukraine has been insane. We used to get breathing room in between disasters to regroup. Not anymore.” Nonetheless, Smarinsky remains mission-focused. “It feels good to be able to help others. I always try to remember that one little individual.”

■ George Spencer

Ali Sadat, DDS '14

Making a Claim on the Future

Mom knows best. When Ali Sadat was in middle school and high school, his mother kept him on an “extremely tight leash,” he recalls. He passed his afternoons doing homework in the back office of the Vacaville, Calif., dental practice where she worked.

Today, he heads Retrace Labs, a San Francisco-based company he founded that uses artificial intelligence (AI) technology to process dental insurance claims, slash office overhead, and speed payouts to patients and practitioners. Launched in 2016 with backing from Sadat’s friends and family, Retrace later received \$18 million in funding from Intel Capital and SoftBank Ventures. Sadat, the company’s CEO, expects the number of dental practices using Retrace to soon balloon from 1,800 to 14,000 and projects a positive cash flow for 2022.

“My adolescent experience was a real eye-opener into today’s challenges. Moving into the profession gave me the technical insights and know-how to solve today’s problems,” says Sadat. That and his multifaceted education, which includes degrees in technology management and bioengineering.

While Retrace faces competition, Sadat says his firm is the only software company to take a holistic approach to the claims process. Dentists using Retrace send insurers X-rays and supporting materials to document a proposed procedure. Then its AI algorithm compares that data to millions of other cases insurers have approved. When the patient arrives for the procedure, the dentist knows their payout and the patient knows their out-of-pocket cost. Insurance company proceeds arrive immediately. “No surprise bills in the mail,” says Sadat.

He marvels at his lifelong connection to UCSF. As an eighth grader, he spent three days there while his mother took dental assistant tests. Even at that age, he knew that a UCSF professor had co-founded the biotech giant Genentech.

Years later, in his UCSF application essay, Sadat wrote that his life’s goal was “to bridge the gap between the benchtop and the bedside.” His mentor was Joel White, DDS. Now a professor emeritus, White was “the original big data and dentistry guy” who played a pivotal role in laying the foundation of today’s work in AI and dentistry, says Sadat.

“If I had been anywhere but UCSF, I wouldn’t be where I am today,” he says. “My mother is incredibly thankful things ended up working out.”

■ *George Spencer*

Amanda Watters Gorman, MS '11

Nurturing Nursing Mothers

Nest Collaborative was born at 2 a.m. when Amanda Gorman struggled, bleary-eyed, to nurse her screaming, hungry infant and – like many mothers before her – found nowhere to turn.

Gorman, a highly educated nurse, was determined to breastfeed both her babies. But in the process, she endured pain; bleeding; inflamed breasts; a baby who failed to thrive; and many sleepless, desperate nights.

She wasn't alone. "I was a child of the '80s. My mom formula-fed me. I had never seen a woman breastfeed," she says. "I'm a pediatric nurse practitioner, and yet I knew nothing about nursing."

After falling out of favor for much of the 20th century – only 22% of mothers breastfed in 1972 – breastfeeding is on the upswing. Now, 83% of new mothers nationwide nurse their newborns. Unfortunately, about a third stop within six months, despite research showing that both moms and babies do better the longer mom nurses.

Experts agree that nursing promotes babies' growth and development – yet where was support for moms unable to afford \$200-plus for a lactation consultant? Gorman was determined to find out. To her surprise, she discovered that breastfeeding support is covered by the Affordable Care Act and has to be provided free to nursing mothers.

So she got busy. With the help of crowdfunding from IFundWomen, Gorman raised \$10,000, formed Nest Collaborative, started helping moms via telehealth, and billed their insurance plans. It was 2017, and few understood videoconferencing. "I was told that women were not going to take their shirts off in front of a computer," recalls Gorman. "To which I responded, 'You've never tried to breastfeed.'"

Her idea gained traction, and when COVID hit in 2020, Gorman was ready. Nest Collaborative went public, raising \$2.1 million of financing in January 2021 and several million dollars more since then. Today, the company serves families in all 50 states, plus military families in Guam, Germany, and Kuwait.

Gorman's advice: Listen to your gut. "No one knows how awful those first few weeks can be. I found myself stuck in a problem ... and I saw a solution. I had to bring it forward."

■ *Katherine Conrad*



Hala Borno, MD, Resident Alum

Ensuring Clinical Trials Serve Patients of Color

As a war refugee, a Palestinian immigrant, and now an oncologist, Hala Borno knows that access to health care can determine whether a patient survives a life-threatening illness – or not.

Cancer outcomes correlate with race and ethnicity partly because clinical drug trials fail to enroll diverse patients – a situation that will only worsen in the era of precision medicine. “It matters who is tested,” she notes.

Borno has witnessed inequities since she was a young child fleeing Kuwait with her family during the first Gulf War. When her grandfather was diagnosed with cancer, she watched her mother struggle to navigate the U.S. health system. As Borno moved through medical training, everywhere she looked she saw barriers to care.

When she realized that racial imbalances have long plagued clinical drug trials – crucial to discovering whether medications are safe and effective, yet serving a fraction of patients who could benefit – Borno had to act.

In 2021, with guidance from UCSF Innovation Ventures, Borno created Trial Library to bring equity to oncology clinical trials; in August, the company emerged from stealth mode, fueled by \$5 million from angel investors attracted by her experience, dedication, and approach.

As a practicing oncologist, Borno knows most patients trust their own doctor: 77% enroll in trials on their doctor’s recommendation. But nearly all cancer patients are treated in community practices – places not commonly involved in clinical trials. So Borno reached out to over 800 oncologists across California to identify the barriers and worked with the drug companies sponsoring trials to overcome them.

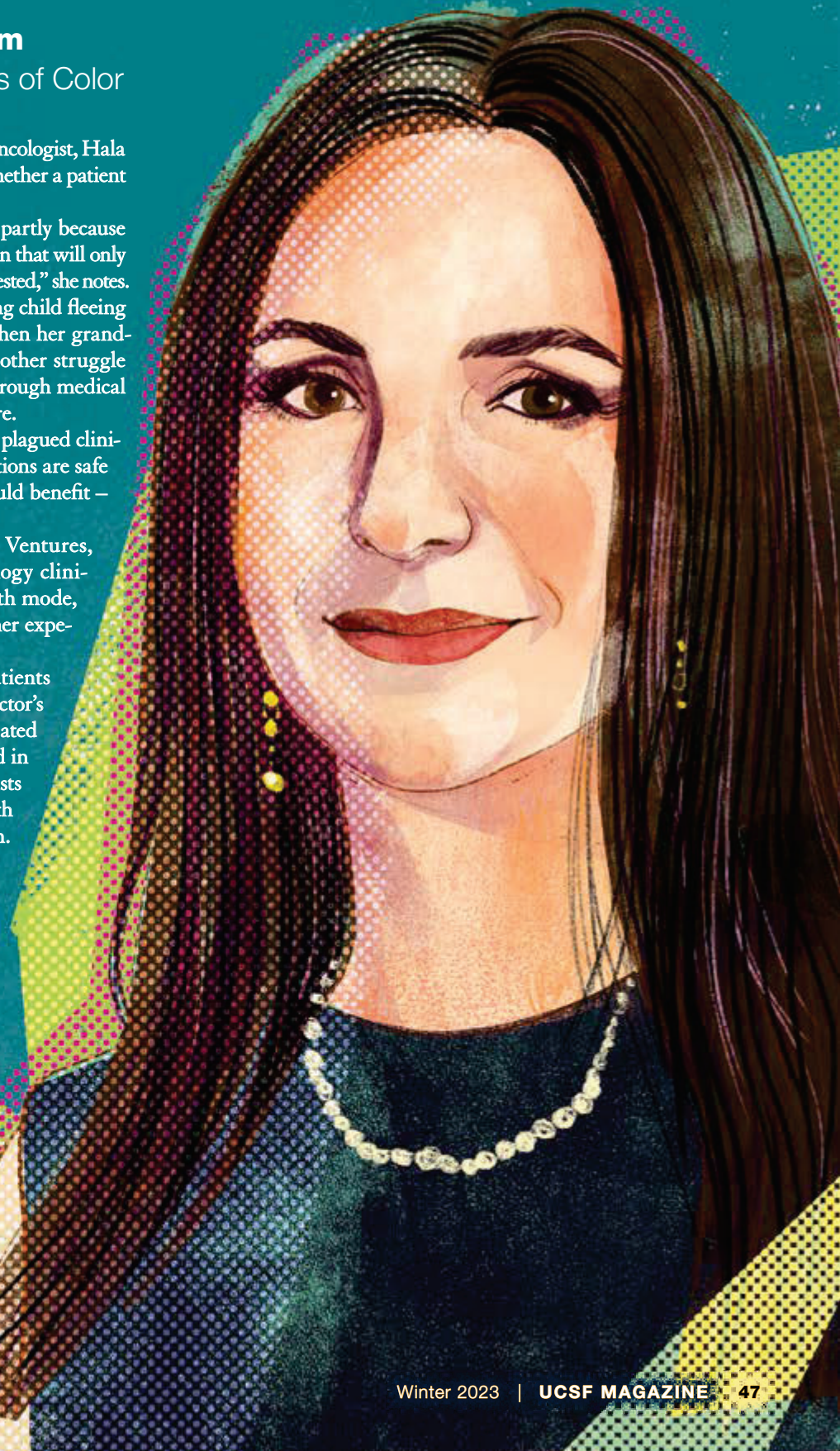
“Our model is very thoughtful,” she explains. “What are the barriers for the medical provider? For the patient?”

Knowing it must be worth doctors’ time to pre-screen patients for trials, Borno offers doctors reimbursement from trial sponsors – a key innovation, it turns out. She addresses patients’ uncertainty by providing navigators to help people enroll. Navigators also evaluate patients’ “social determinants of health” to understand barriers experienced by patients from diverse backgrounds.

Her advice to would-be entrepreneurs? “Listen to that hum in the back of your mind. If it doesn’t go away, do something.”

Now that Trial Library has launched navigation services for cancer trials, Borno plans to tackle racial inequities in trials for other diseases. “Once we fix it in oncology,” she promises, “we can go beyond.”

■ Katherine Conrad



This Must Be the Place: Learning to Make a Home in the World at Every Age

By Stacy Torres, PhD

When I was in my mid-20s, I never planned to study older people. Even when I first met my future research participants – customers five and six decades my senior at the mom-and-pop bakery they and I frequented in Manhattan – I didn’t envision them becoming part of my graduate work. But I soon grew curious about them: about the relationships they formed at the bakery, about why they preferred that setting to a senior center. And soon they were part of my PhD studies in sociology; I decided to conduct a five-year, ethnographic study to understand their experiences aging in place, to follow these longtime bakery customers as they coped with the accumulated losses of neighbors, friends, and family, as well as with gentrification, health setbacks, depression, financial struggles, and other everyday challenges.

I came to see that they’d transformed the bakery into an alternative hub of neighborhood life – a public living room, where they developed the social ties that helped them remain in their homes. Their lessons for survival and belonging continue to enrich my life, teaching me how to make a home in the world wherever I go.

Though three of my four grandparents died before I was born, and I had few opportunities to interact with other older relatives, I shared much in common with the elders I came to know in the bakery. I’d always considered myself an “old soul.” My father and mother, born in 1942 and 1943, were older than my classmates’ baby boomer parents. My sister likened our childhood to growing up with a time machine. Those years made a big difference in shaping my sensibilities, and the music, movies, and experiences my parents introduced me to helped me connect with my research participants.

As lifelong New Yorkers, we engaged in rollicking, no-holds-barred conversations (a communication style that has been astutely analyzed by the linguist Deborah Tannen). Several of us had working-class backgrounds and were the children of immigrants. Many of us had experienced significant loss and illness. As one woman in her late 80s named Sylvia often said, “I’m a veteran without a gun.”

My mother died when I was 16. As her cancer progressed, her world shrank to a one-block radius around our apartment. I helped care for her at home while she was dying. Since my own diagnosis at age 26 with an autoimmune disease, Sjögren’s syndrome, I’ve also adapted to living with chronic fatigue, pain, and symptom “flares.” Like my study participants, I needed even back then to pace myself and interact extensively with health care providers. The elders checked on my health as much as I inquired about theirs.

My ethnographic research helped me manage my own difficult life transitions. While I was conducting the study, I supported my father during a lung cancer recurrence and my sister after a psychiatric

diagnosis and hospitalization. Then my 13-year relationship ended, and I navigated new grief and adjusted to singlehood. Amid these upheavals, I came to San Francisco.

Older people I befriended in the Bay Area soon brought me into their web of care and served as important guides. My roommate, a retired taxi driver from Dublin in his late 70s, played the piano every morning, listened to my ups and downs, and included me in his friendship group of older men, who took me to lunch at the United Irish Cultural Center of San Francisco. Another older friend in the Castro showed me baby owls in Golden Gate Park and drew me into his motley social circle of people he’d met serendipitously in the City. These San Francisco elders faced their own challenges aging in place, including residences on steep hills with stairs not designed for those with mobility problems and a shortage of affordable housing. To cope, they also sought places for connection where they felt comfortable and supported.

In cities like San Francisco and New York, with a rich “public realm” – which the sociologist Lyn Lofland, a UCSF alumna, characterizes as spaces where strangers interact and form relationships – I have been able to implement elders’ strategies to foster a sense of belonging. After my breakup, like many of my study participants, I struggled to fill my weekends. Becoming a regular at different places has helped me assuage loneliness, as I created new routines – spending my Saturdays in North Beach, rotating with other regulars among Caffè Trieste, Caffè Greco, Specs’, and Vesuvio Cafe.

When a study participant named Eugene turned 90, I asked him how quickly his life had passed thus far. He snapped his fingers with a grin – a startling reminder not to waste time, to slow down. Elders have imparted crucial wisdom that has helped me thrive in my later years. I’m now planning for a home where I can grow old with increasing disability, securing a pension and building retirement savings, accessing preventive health care, and advocating for myself in health care settings. I strive for a purposeful life filled with connection as I cultivate different sources of social support.

At 42, I’m firmly ensconced in the “old age of youth.” I try not to lament every new gray hair, wrinkle, and dark spot. I’m grateful to elders for helping me embrace the pleasures of growing older, feel more comfortable in my skin, and accept my mistakes as I learn to approach late life with less fear, judgment, and dread.

Stacy Torres is an assistant professor of social and behavioral sciences in the UCSF School of Nursing.





UCSF Physical Therapy Student Zerrick Santos Wants to Thank You

“I am very grateful to UCSF’s alumni and donors and look forward to becoming a physical therapist who can not only care for an individual patient but also improve their community,” says Santos, who received the first AAUCSF JEDI Scholarship. He is pursuing a doctorate in physical therapy and volunteers at UCSF’s Community Rehabilitation Clinic, which provides free care to uninsured and underinsured patients.

The JEDI Scholarship

The Alumni Association of UCSF (AAUCSF) established the Justice, Equity, Diversity, and Inclusion (JEDI) Scholarship early last year. **To everyone who has made a gift, thank you!**

We aim to double our initial \$125,000 endowment and are now more than halfway to our goal of supporting two UCSF students each year.

Track our progress at
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